# The American Journal of DIGESTIVE DISEASES

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## ORIGINAL CONTRIBUTIONS




Volume 22 June, 1955 Number 6

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| Riboflavin | 10 mg. | Folic acid | 1.5 mg. |
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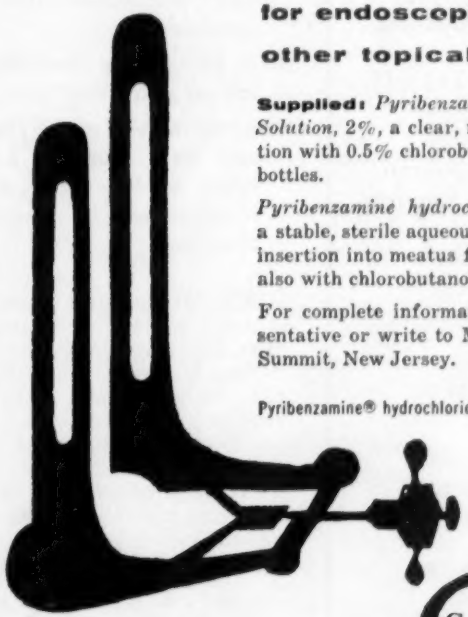

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1. Straughn, R. A.: *Jackson Clin. Bull.*, 13:83, Aug., 1951.
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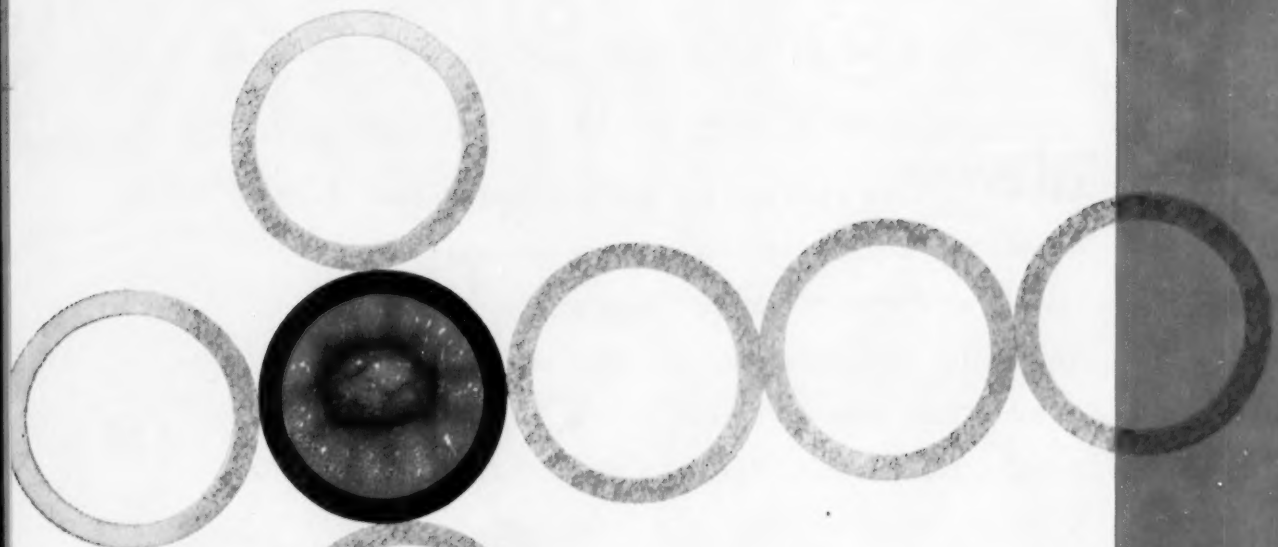

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1. Hoffmann, C. R.: Am. Pract. & Digest Treat. *4*:464, 1953.
2. Riese, J. A.: Am. J. Digest. Dis. *21*:81, 1954.

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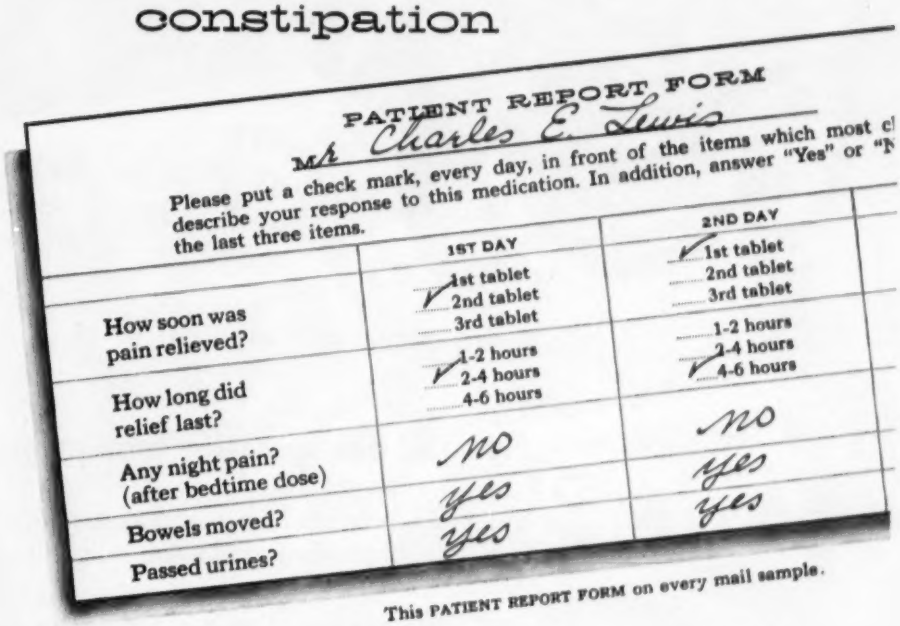

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Mr Charles E Lewis

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describe your response to this medication. In addition, answer "Yes" or "N
the last three items.

| | 1ST DAY | 2ND DAY | |
|---|---|---|---|
| How soon was pain relieved? | ✓ 1st tablet<br>2nd tablet<br>3rd tablet | ✓ 1st tablet<br>2nd tablet<br>3rd tablet | |
| How long did relief last? | ✓ 1-2 hours<br>2-4 hours<br>4-6 hours | 1-2 hours<br>2-4 hours<br>✓ 4-6 hours | |
| Any night pain? (after bedtime dose) | no | no | |
| Bowels moved? | yes | yes | |
| Passed urines? | yes | yes | |

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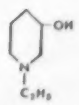


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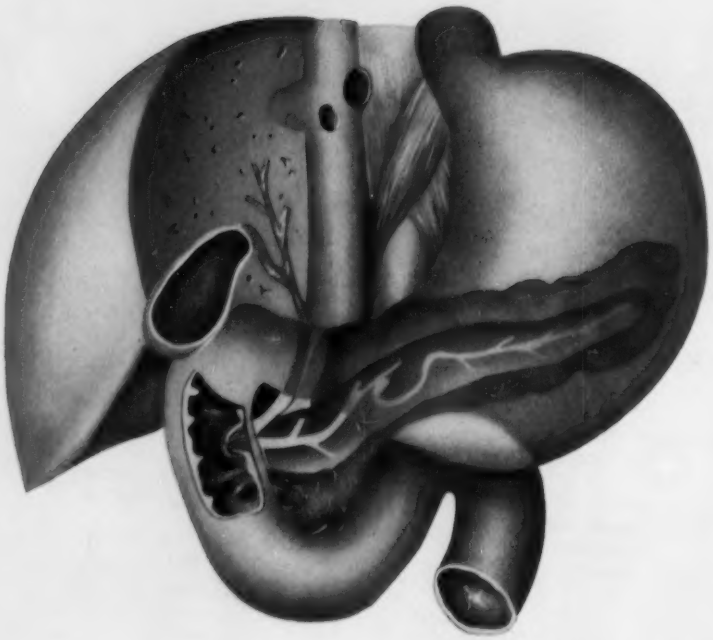

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ORAL SUSPENSION (fruit flavored)
125 mg./5 cc. teaspoonful

**The minimum daily dose of each antibiotic** ***(1 Gm. of Terramycin or Tetracyn, or 600,000 units of penicillin)***
**Stress Fortifies the patient** ***with the stress vitamin formula*** **recommended by the National Research Council:**

| | | | |
|---|---|---|---|
| Ascorbic acid, U.S.P. | 300 mg. | Calcium pantothenate | 20 mg. |
| Thiamine mononitrate | 10 mg. | Vitamin $B_{12}$ activity | 4 mcg. |
| Riboflavin | 10 mg. | Folic acid | 1.5 mg. |
| Niacinamide | 100 mg. | Menadione (vitamin K analog) | 2 mg. |
| Pyridoxine hydrochloride | 2 mg. | | |

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# CLINICAL STUDY ON WEIGHT REDUCTION IN OBESITY

H. SAPOZNIK, M. D.,* Chicago, Illinois.

WEIGHT REDUCTION is relatively easy if a person has the stamina to live on a reducing diet first and then on a restricted diet for a long period of time. However, in most obese persons the will-power to reduce food intake is absent or limited. Therefore, in such cases it becomes necessary to strengthen the patient's determination to follow doctor's orders. As long as we do not know how to specifically affect a center in the brain which regulates food intake, we will not be able to treat obesity specifically.

The average obese person has a normal basal metabolic rate and normal endocrine functions. Obesity is often followed, however, by hypertension and, in a number of cases, it leads to diabetes. It is desirable, therefore, for the physician to treat obesity before harmful complications develop.

Pronounced infiltration of the liver with fat, in the presence of obesity, has been reported by Zelman (1). It is probable, therefore, that some metabolic functions of the liver are disturbed in obese subjects. Hence, frequent clinical complaints of the obese, such as lassitude, headaches, and constipation, may be related to the liver. Since infiltration of the liver with fat is abnormal, it should be treated. Thus, in obese persons, a clinical trial with lipotropic substances may be indicated.

The use of vitamins for increasing a sense of well-being in certain conditions is well known. If vitamins would increase a sense of well-being and activity in the obese, the subject would be more active, use up more calories, and lose his lassitude and passivity which prevents him from disciplining himself to follow doctor's orders. For these reasons, a number of drugs have appeared which combine lipotropic agents with vitamins.

In many of these drugs, a small quantity of amphetamine is employed in order to depress hunger and to overcome lassitude, and a small amount of sedative is incorporated to diminish tension and nervousness often occurring under a strict dietary regime, or associated with amphetamine administration. Some compounds contain methylcellulose or similar bulk-producing material, in order to induce a feeling of satiety. In other combinations of drugs, belladonna alkaloids are used to diminish strong hunger contractions of the stomach and other gastro-intestinal complaints, which seem to occur when a restricted diet is instituted.

The present study on a group of private patients was conducted in order to compare the effects of six different formulas of reducing compounds in order to find the most satisfactory one. The compounds used were:

A: Proloid 0.5 grains
Benzedrine 5 mgm
Extract of belladonna 1/20 grain
Phenobarbital ¼ grain
1 capsule ½ hour before each meal (t.i.d.)

B: Proloid 0.75 grains
Benzedrine 7.5 mgm
Extract of belladonna 1/20 grain
Phenobarbital ¼ grain
1 capsule ½ hour before each meal (t.i.d.)

C: Proloid 1 grain
Benzedrine 10 mgm
Extract of belladonna 1/20 grain
Phenobarbital ¼ grain
1 capsule ½ hour before each meal (t.i.d.)

D: Dexedrine with prolonged action, 10 mgm
Phenobarbital 1 grain
1 before beakfast

E: Dexedrine with prolonged action, 15 mgm
Phenobarbital 1 grain
1 before breakfast

F:* d-Amphetamine sulfate 5 mg
Phenobarbital 16 mg
dl-Methionine 150 mg
Choline Bitartrate 400 mg
Vitamin $B_{12}$, U.S.P., 4 mcg
Methyl Cellulose 160 mg
Magnesium Stearate 14.18 mg
1 capsule 30 minutes before every meal (t.i.d.)

All patients were asked to use a 1,000 calorie diet containing approximately 100 grams of carbohydrate, 20 grams of fat, and 100 grams of protein. The procedure with the patients was to begin with formula A and to increase the dosage of formula A gradually up to that of formula C. If formula A was not indicated, or if it produced side-reactions, formula D was employed and eventually increased to formula E.

Formulas A to E were found unsatisfactory in a large percentage of patients. The side effects noted were nausea, epigastric distress, nervousness, insomnia, dizziness, headaches, palpitations, and constipation. These symptoms appeared in 12 out of 16 patients on formula A to C and in 10 out of 14 patients on formula D or E. With formula F, only 2 patients complained about insomnia, nausea, and epigastric distress. However, these symptoms were slight, and the patients were able to continue on formula F, the complaints disappearing within a few days. Fourteen out of 16 patients in group F reported a feeling of relaxation and ease, while only 4 patients in each of the former groups reported this feeling. All patients on formula F improved in their general attitude and reported that they felt much better under the present therapy. The patients became cooperative, and more so as they improved. The results with formula F are demonstrated in *Table 1*. It is seen that in every patient with hypertension, the loss of weight was accompanied by an average decrease

*104 South Michigan Avenue, Chicago, Illinois.

*Obolip, Lakeside Laboratories, Inc., Milwaukee, Wisconsin. We are obliged for a liberal supply of the preparation.

TABLE I

EFFECTS OF OBOLIP DURING A 6 WEEK PERIOD OF TREATMENT

| Case No. | Sex M,F | Age Years | Basal Metab. % | Pulse p. Min. | Blood pressure mm Hg Before | After | Hemogl. % | Blood Red Blood Count Millions | White Count | Bodyweight in Pounds Before | After | Loss |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | | 22 | + 9 | 96 | 160:96 | 134:80 | 86 | 4.8 | 4000 | 158 | 136 | 22 |
| 2. | | 29 | + 3 | 90 | 110:76 | | 14.6 g | 4.8 | 5900 | 160 | 147 | 13 |
| 3. | | 40 | − 9 | 86 | 200:130 | 160:90 | 87 | 4.9 | 8540 | 194 | 182 | 12 |
| 4. | | 49 | − 4 | 76 | 196:110 | 144:80 | 90 | 4.6 | 6700 | 182 | 167 | 15 |
| 5. | | 57 | −14 | 86 | 186:102 | 140:80 | 96 | 5.2 | 8000 | 197 | 172 | 25 |
| 6. | | 39 | − 1 | 84 | 176:100 | 130:82 | 100 | 4.9 | 6200 | 174 | 164 | 10 |
| 7. | | 45 | + 4 | 80 | 136:88 | | 87 | 4.8 | 7400 | 168 | 133 | 35 |
| 8. | | 50 | +12 | 84 | 112:76 | | 87 | 4.1 | 7000 | 160 | 147 | 13 |
| 9. | | 56 | +10 | 76 | 169:90 | 130:80 | 84 | 4.2 | 8000 | 164 | 150 | 14 |
| 10. | | 44 | − 4 | 88 | 146:96 | 118:80 | 86 | 4.8 | 8100 | 171 | 148 | 23 |
| 11. | | 18 | −14 | 96 | 104:80 | | 86 | 4.2 | 7600 | 155 | 139 | 16 |
| 12. | | 53 | − 6 | 90 | 146:100 | 120:80 | 84 | 4.1 | 5100 | 174 | 160 | 14 |
| 13. | | 43 | + 1 | 84 | 166:96 | 132:80 | 90 | 4.9 | 9100 | 151 | 134 | 17 |
| 14. | | 32 | − 3 | 84 | 130:80 | | 94 | 4.9 | 9700 | 263 | 235 | 28 |
| 15. | | 30 | −10 | 76 | 130:80 | | 95 | 4.8 | 6800 | 222 | 191 | 31 |

in systolic blood pressure of 38 mm and in diastolic blood pressure of 21 mm. The average weight loss during the 6 week period of therapy was 19 pounds, or approximately 3 pounds per week. In our experience, a slow rate of weight loss is better than a rapid one, and 3 pounds per week appears not to be detrimental to the health and well-being of the patient. With the improvement of blood pressure, most patients reported that headaches and dizziness had either disappeared or become less. They also showed a strengthening of self-discipline after several weeks of treatment, which made it easier for them to adhere to dietary restrictions.

An additional 5 patients, not shown in the table, lost 4 to 6 pounds during a period of 2 weeks of therapy on formula F.

## DISCUSSION

It is revealing that a reducing drug, designed to deal metabolically with the hepatic pathology (fatty infiltration) associated with obesity, was considerably more successful in aiding weight reduction than agents containing central nervous system stimulants alone or in combination with thyroid preparations. Permitting speculation, it appears that attention to normal hepatic function is more significant in the management of obesity than an increased metabolism such as produced by thyroid medication.

The fact that drugs containing a central nervous system stimulant, such as the amphetamine derivatives alone or in combination with thyroid extracts, do not produce the desired results in weight reduction without undesirable side effects, is in contrast to the reasonably uniform and predictable manner in which a reducing agent containing lipotropic agents for the treatment of fatty infiltration of the liver appears to work. Thus, the claim of "a metabolic approach to obesity" made for Obolip is supported by clinical experience.

## SUMMARY AND CONCLUSIONS

Six different formulas were tried out on patients in order to induce decreased food intake and permit weight reduction.

Benzedrine or Dexedrine, by themselves or in combination with thyroid hormone, produced loss of weight, but also a number of undesirable side effects.

The best reducing combination was a preparation (Obolip) which contains only a small dose of d-Amphetamine, a small dose of phenobarbital, lipotropic factors, vitamin $B_{12}$, and methylcellulose. With the latter compound, a few mild side-reactions which disappeared with continued therapy, were noted in 2 out of 15 cases. An average weight loss of 3 pounds per week during a 6-week period of medication, was produced during Obolip therapy.

## REFERENCES

1. Zelman, S.: The liver in obesity. Arch. Intern. Med., 90: 141-156, 1952.

# AN EFFECTIVE THERAPEUTIC APPROACH TO THE CONTROL OF ATHEROSCLEROSIS ILLUSTRATING HARMLESSNESS OF PROLONGED USE OF THYROID HORMONE IN CORONARY DISEASE

MURRAY ISRAEL, M. D., New York, N. Y.

THIS STUDY describes in detail our method of approach to the problem of atherosclerosis. As the control of coronary atherosclerosis is by far the most difficult, we shall first discuss an illustrative case report and outline twenty similar ones. The important facets forming the background of this approach are reviewed, namely: the theoretical considerations; the standardization of oral therapy (1946, 1948); the introduction and standardization in 1952 of a new parenteral hormone-vitamin compound; the use of cholesterol determinations; and, finally, the criteria used to evaluate results in the treatment of the metabolic factor in chronic disease.

## CASE REPORT

E. H., a white male, age 46 years old when first seen on September 20, 1949. E. H. is a typical New Yorker, exposed to the stresses and strains of the highly complex, competitive life of the metropolitan area. The family history reveals that his father died at 70 of coronary thrombosis, and that three uncles died at various ages of coronary disease. E. H. had his first coronary occlusion 7½ years previously (April 1942). The exact date of his second occlusion is not known. His chief complaint was precordial distress at the slightest exertion. Associated complaints included: fatigue, nervousness, irritability, headache, leg pains, numbness of hands, heartburn "in the middle of the night, relieved by two alka seltzers," post-prandial distension, excessive thirst at intervals, and an irritating tinea cruris for two years.

The relevant physical findings, early in 1950, were:

*Cardiac:*

"(1) Coronary arteriosclerosis with bimural myocardial infarctions, old, involving the posterior and anteroseptal walls; coronary insufficiency, moderate, evidenced by the positive exercise test.

"(2) Occlusive arterial disease, probably arteriosclerotic in origin, moderate arterial insufficiency involving the right lower extremity, evidenced by intermittent claudication, coolness, and absence of pulsation in the popliteal, posterior tibial and peroneal arteries."†

*Other Findings:* Enlarged liver, patchy vascular calcifications (leg arteries bilaterally); marked cervical arthritis.

*Blood Chemistry:* Cholesterol-phospholipid ratio, 355/347.

## TREATMENT

The phrase "standarized therapy" employed throughout this article requires an explanation: In 1946, after the optimum vitamin amounts which seemed most effective in stimulating the oxidative processes had been found by trial and error, we arrived at a definite combination, quantitative and qualitative, which was to be administered with thyroid. This we called Oxytropin*(2). In 1948 the same procedure was followed with Lipotropin**(2); and in 1952 with Co-Thyro-Bal-d*** This "standardization" made it possible for us to avoid the confusion caused by the use of the hundreds of different B-complexes which were on the market at that time. The mixtures, although containing multiple vitamin factors, were in constant ratio one to another, and enabled us to have a relatively constant measurable (although empirical at that time) from which better to evaluate therapeutic results.

E.H. was placed on the standard therapy outlined below:

1. A high protein-low cholesterol diet.

2. *Oxytropin T-15 was given three times a day with meals for two weeks, and then Oxytropin T-20 three times a day. The dose of Oxytropin was increased every two weeks until it reached T-50, where it remained for one month. Finally, the patient was given Oxytropin T-60, which has been his maintenance dose for over five years.

3. **Lipotropin: For the first three months he received ten tablets of Lipotropin three times daily with meals. Total dosage per day was: choline hydrochloride, 12660 mg., inositol, 4020 mg., and pyridoxine hydrochloride, 60 mg. For the next three months the dose was reduced to five tablets three times daily with meals. After six months, the dose was reduced to four tablets three times daily with meals, which has been his maintenance dose for five years.

4. ***Co-Thyro-Bal-d: This has been administered intravenously since 1952. The evolution and administration of this compound will be discussed below.

†Courtesy of Dr. George P. Robb.

Instructor in Medicine, New York Medical College, Flower and Fifth Ave. Hospitals.

*OXYTROPIN is a combination of thyroid extract in varying amounts, with the oxytropic B factors plus ascorbic acid. Only the amount of thyroid varies, and, for convenience the letter "T" is followed by a numeral (10, 12, 15, 20, 30, 40, 50, and 60 mg.) indicating the amount of thyroid extract per dose. The vitamin factors remain constant: riboflavin, 10 mg.; niacinamide, 120 mg.; thiamin chloride, 20 mg.; ascorbic acid, 100 mg.

**LIPOTROPIN: Each oral tablet contains: choline, 422 mg.; inositol, 134 mg.; pyridoxine hydrochloride, 2 mg. The dose for the patient varies from one to ten tablets, three times daily with meals. This dosage is determined empirically—the greater the amount of atheromatosis, the larger the number of tablets.

***CO-THYRO-BAL-d: *Development*: From 1947 to 1952 we searched for a thyroid-vitamin combination which given parenterally would affect cholesterol metabolism. At first, a mixture of liver extract and thyroxin was injected intramuscularly, and in 1949, Crude B 12 was substituted for liver

### PROGRESS

Within a few months, *all* of the symptoms—precordial distress, tiredness, nervousness, etc.—were ameliorated. The former working capacity, optimism, perspective and sense of humor returned. Objectively, the patient looked well—and was reminded of his illness only after running a block; then slight precordial distress was experienced, but disappeared almost immediately when he stopped running.

In view of the fact that no formal psychotherapy was given, his improvement had to be attributed to the treatment of the metabolic factor. General improvement continued, although his average cholesterol levels changed only moderately. The level had fallen from an initial 355 mg. to 174 mg. within six weeks, but had gone back toward 300 very soon after, fluctuating between 209 and 293 in 1950; between 209 and 309 in 1951.

The cholesterol pattern shown on the chart below is unique in that it includes more than 150 cholesterol readings in the past 5½ years.

| | *No. of Readings* | *Average* | *High(H)* | *Low(L)* |
|---|---|---|---|---|
| 1949 | 6 | 274.0 | 355 | 174 |
| 1950 | 20 | 259.8 | 293 | 209 |
| 1951 | 21 | 256.1 | 309 | 209 |
| 1952 | 30 | 233.6 | 315 | 180 |
| 1953 | 43 | 203.6 | 262 | 153 |
| 1954 | 32 | 216.5 | 262 | 153 |

(See Diagram Illustration on Page 166).

A glance at the cholesterol pattern indicates a definite stabilization of the blood cholesterol levels at a lower and narrower range since late 1952. How was this accomplished? We—and others (12) (13)—have for many years noted that, despite symptomatic improvement in the large majority of patients under this type of therapy, there would be a return toward the pre-treatment cholesterol levels after the initial drop. Although cholesterol levels with oral Oxytropin-Lipotropin factors alone could be maintained in some patients at fairly stabilized low levels, most patients on oral therapy had a cholesterol pattern which showed wide fluctuations.

CTB-d (Co-Thyro-Bal-d), in the chart above, was injected thirty times during the year 1952. The fall of the average cholesterol level from 256 to 233.6 mg. is noteworthy. Owing to a real general improvement with the new compound, the patient was extremely cooperative in determining whether additional CTB-d would produce even more favorable results. The outcome is evident in his cholesterol picture in 1953, when 43 doses of CTB-d (each dose equivalent to one mg. laevo thyroxin) were administered, and his average cholesterol level then fell from 233.6 to 203.6, and his cholesterol range fluctuated between 262 and 153. In 1954, when only thirty-two determinations were obtained, a slight rise to an average of 216.5 mg. occurred. It seems reasonable to assume, then, that the administration of throxin can be accomplished by means of Co-Thyro-Bal-d without toxic effects, especially since similar results have been obtained on several hundred other patients.

On January 8, 1955, E. H. was re-examined by the same cardiologist who had given his report almost five years before. E. H.'s present status is as follows:

*Report from Dr. George P. Robb, M. D.*

"I examined Mr. E. . . . . H. . . . . and found his cardiovascular status to be much better than it was when I previously examined him, almost five years ago. He now has no complaints, although on questioning he admits he experiences a mild 'pressure feeling' in the chest after running one block. This is not brought on by climbing several flights of stairs or by climbing hills near his Connecticut home, both of which he does several times a day. He has no leg pain, cramp or symptoms suggestive of intermittent claudication . . . .

"On physical examination there was definite objective evidence of improvement in the circulation to the right lower extremity. The radial, brachial, femoral popliteal, dorsalis pedis and posterior tibial arteries were all palpable and pulsated normally. The right posterior tibial pulsation was not as strong as the left one . . . . . (Previous examination—no pulsation.)

"The exercise tests of coronary adequacy . . . . . were not strictly comparable since the previous one terminated prematurely because of leg pain after the completion of only 28 of the prescribed 42 ascents. However, the changes induced by the smaller amount of exercise five years ago and by the standard amount at this time are about equal, suggesting improvement in coronary blood flow . . . . .

"In general, there has been definite objective improvement in the circulatory status of the right lower extremity, and, I believe, definite, though less marked improvement in the coronary circulation . . . ."

This excerpt reporting obvious improvement in the cardiovascular system of a patient after more than five years of hormone-vitamin therapy, is doubly suggestive since the source was completely disinterested. Whether a decholesterolization took place in this man, whether his improvement was caused by better sympathetic-parasympathetic balance, or by any other known or unknown factors, cannot be definitely proven. The significant facts are that his readjusted metabolism has been accompanied by steady improvement and that this type of result occurred in a high percentage of patients with similar problems, twenty of whose cases are tabulated below:

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extract. No beneficial effect was observed at that time among the patients receiving it, and the search was continued when B 12 crystalline became available in 1950. The latter was mixed with thyroxin and administered intravenously for the first time. It required more than a year to find the dosage and frequency of administration necessary to help stabilize the cholesterol metabolism and to make possible standardization of what has proven spectrophotometrically to be a new compound.

*The method of preparation of Co-Thyro-Bal-d* is as follows: Equal parts of sodium thyroxin and crystalline B 12 are dissolved in pyrogen-free water and the reaction permitted to occur. The resultant solution is buffered to pH 10. As the coordination compound formed is unstable, the solution is immediately lyophilized. Although the formula of B 12 crystalline is not available, perhaps the amine group of the thyroxin is attached to B 12 by the replacement of the cyano group.

| | A. M. G. | J. R. | R. W. | G. I. | M. A. | J. M. | C. P. G. |
|---|---|---|---|---|---|---|---|
| Age-Sex | M-52 | M-46 | M-41 | M-55 | M-49 | M-66 | M-54 |
| EKG Findings | Neg. | Pos. | Pos. | Pos. | Pos. | Pos. | Pos. |
| Duration of Symptoms | | | | | | | |
| Before Rx | 24 mos. | 76 mos. | 15 mos. | 24 mos. | 12 mos. | 16 mos. | 24 mos. |
| After Rx | 2 mos. | 1 mo. | 5 mos. | 6 mos. | 6 mos. | 3 mos. | 1 mo. |
| Duration of Rx | | | | | | | |
| Oral | 75 mos. | 74 mos. | 63 mos | 60 mos. | 56 mos | 55 mos. | 53 mos. |
| CTB-d | 34 mos. | 37 mos. | 36 mos. | 33 mos. | 30 mos. | 33 mos. | 32 mos. |
| Maintenance-CTB-d* | 1.0(4) | 1.5(1) | 1.0(4) | 0.5(2) | 1.0(4) | 0.5(1) | 0.5(4) |
| Cholesterol | | | | | | | |
| Total Readings | 54 | 102 | 131 | 110 | 65 | 90 | 65 |
| Initial Reading | 377.0 | 486.0 | 248.0 | 270.0 | 444.0 | 255.0 | 269.0 |
| Average before CTB-d | 259.0 | 404.0 | 230.4 | 223.3 | 240.0 | 153.2 | 188.4 |
| Average after CTB-d | 228.7 | 366.7 | 211.8 | 200.4 | 219.2 | 154.5 | 193.9 |

| | E. M. | J. L. I. | J. S. | D. F. | A. N. | M. J. | A. W. |
|---|---|---|---|---|---|---|---|
| Age-Sex | F-37 | M-57 | M-52 | M-53 | M-46 | M-56 | M-42 |
| EKG Findings | Pos. | Pos. | Neg. | Pos. | Pos | Neg. | Pos |
| Duration of Symptoms | | | | | | | |
| Before Rx | 6 mos. | 60 mos. | 7 yrs. | 4 mos. | 5 wks. | 3 mos. | 21 mos. |
| After Rx | 3 mos. | 1½ mos. | 7 mos. | 1 mo. | 2 mos. | 18 mos. | 8 mos. |
| Duration of Rx | | | | | | | |
| Oral | 51 mos. | 47 mos. | 39 mos. | 38 mos. | 38 mos. | 33 mos. | 32 mos. |
| CTB-d | 32 mos. | 28 mos. | 31 mos. | 36 mos. | 29 mos. | 31 mos. | 32 mos. |
| Maintenance-CTB-d | 0.8(3) | 0.6(4) | 0.5(2) | 1.0(2) | 0.5(2) | 0.5(2) | 1.0(2) |
| Cholesterol | | | | | | | |
| Total Readings | 64 | 58 | 54 | 61 | 51 | 58 | 56 |
| Initial Reading | 253.0 | 277.0 | 345.0 | 174.0 | 248.0 | 209.0 | 300.0 |
| Average before CTB-d | 236.1 | 203.5 | 262.6 | 184.5 | 216.2 | 170.0 | — |
| Average after CTB-d | 214.1 | 167.2 | 218.7 | 180.8 | 191.1 | 171.9 | 237.0 |

| | B. O. | A. K. | E. D. S.** | H. G.** | C. G. | G.V. |
|---|---|---|---|---|---|---|
| Age-Sex | M-46 | F-45 | M-54 | M-51 | M-62 | M-51 |
| EKG Findings | Pos. | Neg. | Neg. | Pos. | Pos. | Pos. |
| Duration of Symptoms | | | | | | |
| Before Rx | 72 mos. | 24 mos. | 4 days | 24 mos. | 3 mos. | 6 mos. |
| After Rx | 2½ mos. | 6 wks. | Persists | Persists | 6 wks. | 3 wks. |
| Duration of Rx | | | | | | |
| Oral | 30 mos. | 30 mos. | 12 mos. | 11 mos. | 6 mos. | 3 mos. |
| CTB-d | 30 mos. | 30 mos. | 12 mos. | 11 mos. | 6 mos. | 3 mos. |
| Maintenance-CTB-d | 1.0(4) | 0.5(2) | 1.0(2) | 1.0(2) | 0.5(2) | 0.5(2) |
| Cholesterol | | | | | | |
| Total Readings | 37 | 48 | 22 | 22 | 11 | 8 |
| Initial Reading | 300.0 | 300.0 | 300.0 | 315.0 | 327.0 | 284.0 |
| Average before CTB-d | — | — | — | — | — | — |
| Average after CTB-d | 236.2 | 192.8 | 237.9 | 199.0 | 234.0 | 213.4 |

*Note: Numeral in () after CTB-d = number of weeks between injections.
**H. G. and E. D. S. have improved but are not completely symptom-free.

Before the discussion of this study it may be advisable to describe the important factors which form the background of this approach to the control of atheromatosis:

## I. THEORETICAL CONSIDERATIONS

In the last decade some of the major advances in the field of arteriosclerosis were initiated by the development of the anoxemia theory of arteriosclerosis proposed by Hueper (1). Through an analysis, coordination and integration of the numerous and varied clinical, pathologic and experimental data dealing with the different types of arteriosclerotic disease, this investigator concluded that the common fundamental action through which the various types of causal agents and their different causal mechanisms affect the vascular

walls is represented by a severe and short, or a moderate and prolonged, but frequently recurring or persistent interference with the oxidative metabolism and nutrition of the vascular wall. Although atherosclerosis is by far the most common and deadly type of arteriosclerosis, it is paradoxically the most amenable to therapy, for the following reasons:

(a) Although all the facets connected with the reason for the so-common lipoid deposits of the arterial intima which play the important role in the production of atherosclerosis are not known in their entirety, it is not necessary to know these with absolute certainty in order to formulate a therapy, if we keep in mind the following deductions: first, that atherosclerosis results from the failure of the organism to prevent precipitation of exogenous and/or endogenous cholesterol; second, that this failure is the result of the derangement, cyclic or persistent, of the hormonal control of the oxidative cellular metabolism; third, that the key to this derangement is thyroid hormonal dysfunction (hereditary and/or acquired);

(b) the present availability, for therapeutic use, of known anti-atherosclerotogenic agents, i.e., thyroid hormone, oxytropic and lipotropic factors of the vitamin B complex;

c) the availability of a measuring rod, namely, the charting of blood-cholesterol levels. This method of study, although inadequate and at times confusing, makes it possible to measure the effect of therapeutic agents directed at improving the oxidative and lipoid metabolism, and at correcting the quantitative and qualitative abnormalities of the blood plasma. To be of any value in clinical research, many cholesterol determinations on the same patient must be made over a long period of time. Only then can inferences be drawn from any constant change in the pattern.

## II. Standardization of the Therapeutic Management

In 1948 our group decided to concentrate our efforts on a clinical research program, using an approach which could be applied to a large majority of patients, which would form a rounded structure of therapy, and which would be reproducible. The therapeutic management was and is based on the following considerations:

(a) *Diet*: A diet rich in proteins and poor in fat and calories decreases the tendency toward dietary hypercholesterolemia. It may increase the colloidal stability of the plasma lipoids by providing adequate amounts of proteins for the formation of plasma albumins which serve as colloidal stabilizers of lipoids of the plasma. A diet with an abundant protein content, moreover, stimulates the general metabolic processes and thereby depresses metabolic abnormalities which might be involved in the excessive plasma cholesterol content.

(b) *Stimulation of the Oxidative Metabolism (3):* Thyroid hormone and the oxytropic factors of the vitamin B complex (thiamin, riboflavin, niacinimide, in combination with ascorbic acid) activate intracellular and extracellular oxidative processes and thereby stimulate metabolization of cholesterol, suppressing at the same time any tendency toward hypercholesterolemia.

Method of Administration: It had been found (2) empirically that thyroid extract had to be administered in most instances in gradually increasing amounts, starting usually with 10 mg. three times daily and reaching a maintenance dose after a few months. The combination used in this study was standardized in 1946 and described previously (*Oxytropin).

(c) *Mobilization of Cholesterol from Tissue Depots (4):* Experimental observations and clinical investigations indicate that choline, inositol and pyridoxine under certain circumstances mobilize fat and lipoids from tissue depots (and prevent the deposition of excessive fat within tissues).

In 1948, a formula containing lipotropic factors—choline, 422 mg.; inositol, 134 mg.; pyridoxine hydrochloride, 2 mg.—was standardized. The dosage for the patient varies in the manner previously described.

We thus began the clinical research program in 1948 with three fairly definite measurables: high protein-low cholesterol diet, Oxytropin, Lipotropin. These therapeutic factors have not been changed in the past six years and provide a constant set of measurables to be applied to the most complex of creatures—human patients—who differ as to heredity, diet, and exposure to environmental influences; who differ in intellect, experience and attitude; who differ in blood findings, x-ray findings and symptomatology. It must be borne in mind at all times that when we attempt to deal with the metabolism of an individual, we are confronted by an infinitude of possible metabolic variations within each patient, and from patient to patient. We wish to repeat and emphasize that the standardization of these multiple factors which occurred in 1946, 1948 and again in 1952, was a procedure which was necessary to bring some order out of the therapeutic chaos associated with the problem of atheromatosis.

## III. Blood Cholesterol Determinations

A short review of the importance of quantitative cholesterol measurements is indicated. More than 30,000 blood cholesterol readings have been used in this study. The following definite impressions can be noted as to the meaning of these readings, which are done periodically (every week or two, or monthly) on all patients under observation. A single reading, unless extremely high or low, rarely has any significance and may be misleading. We have divided the various individual patterns into five different groups, based purely on the quantitative considerations:

(a) *Essential Xanthomatosis:* This hereditary type, although rare, is a definite proof of the marked hereditary factor which determines such an individual's cholesterol level. As only a quantitative cholesterol measurement will clinch the diagnosis of essential xanthomatosis, every patient should have one or two cholesterol determinations. Thus, single cholesterol measurements (above 375) have their value diagnostically in this hereditary endogenous hypercholesterolemia.

(b) *Hypercholesterolemia:* Any reading between 250 and 375 is arbitrarily placed in this heading. We have found two main types of hypercholesterolemia: (1) *the steady type,* in which the level is lowered with great difficulty and which we feel has a large hereditary factor, is closely related to essential xanthomatosis, and prob-

ably belongs in the milder varieties of this group; (2) *the fluctuating type,* in which the cholesterol shows marked fluctuations from week to week, and probably from day to day. It is from this group that we can learn most about factors which affect cholesterol metabolism. (The patient described above in detail belongs to this group.) It is obvious that any cholesterol pattern which is unstable for a few years, and suddenly becomes stabilized at a lower and narrower range on addition of a new therapeutic agent, is at present the most useful of all criteria for clinical research.

(c) *The so-called "normal" cholesterol pattern:* We have placed any continuous set of cholesterol readings between 180 and 220 in this pattern. There are many individuals who maintain a "normal" cholesterol pattern throughout therapy. Actually, this pattern is what we try to obtain in the treatment of the hypercholesterolemia group. This so-called "normal" pattern has been the cause of most of the previous confusion regarding cholesterol, because many patients with these average readings have severe atherosclerosis while others have no atherosclerosis. The individual scientist who did most to clarify this confusing paradox was Dr. John W. Gofman, whose brilliant achievement with the ultracentrifuge elucidated the problem by the discovery of qualitative differences in the cholesterol molecules (5) (6) (7) (8). His lipoprotein refractive index clarified the most controversial, most difficult and least understood aspect of the cholesterol mechanism and adds some support to the validity of the anoxemia theory of Hueper.

(d) *The hypocholesterolemia pattern* (75 to 140) is the last arbitrary group. Only a small percentage of patients fall into this group.

## IV. Introduction of Co-Thyro-Bal-d Parenteral Therapy

The story of Co-Thyro-Bal-d has been related in the progress report of E. H. It is our opinion that CTB-d is the key to intravenous thyroxin therapy. After experience with thousands of such intravenous injections for over three years, there has been no sign of any thyroid toxicity. E. H.'s cholesterol pattern illustrates the manner in which new therapeutic agents can be added in this type of approach and their effects measured indirectly. This report will not touch on theoretical reasons for the lowering and stabilization of blood cholesterol levels. That this effect is related to a fundamental adjustment of the thyro-pituitary-adrenal axis is probable. More experience with this potent therapeutic agent will be needed, and better methods of measuring steroid metabolism must become available before final judgment can be made. However, many thousands of injections of Co-Thyro-Bal-d on several hundreds of patients have left us with the following impressions:

(a) CTB-d is a potent factor in speeding up the readjustment of the metabolism (esp. lipoid) of a large majority of patients.

(b) It makes possible more rapid attainment of the oral maintenance dosage of Oxytropin and Lipotropin.

(c) It prevents the return to pre-treatment cholesterol levels in a sizable proportion of hypercholesterolemia patients.

(d) It creates a profound metabolo-psychic effect on the large majority of patients, as evidenced by amelioration of the symptoms usually associated with the stress and strain of our present civilization—tension, irritability, nervousness and depression. This indicates an improvement in oxidative metabolism, over and above that obtained by oral therapy alone.

In a small percentage of the patients, despite improvement in general symptomatology, there is no marked reduction of hypercholesterolemia levels. This indicates that Co-Thyro-Bal-d is not the complete answer to this complex problem, or that we have not yet discovered all the facets in its administration.

We have now reviewed the theoretical and actual facets of the approach to the attempted control of atherosclerosis. In assessing our results it has been necessary to establish new criteria. In order to show the firm foundation for these criteria, it may be pertinent at this time to discuss the background of the problems which had to be overcome.

*Lack of Controls:* Although some investigators have used human controls, we have found it impossible in the therapy of atherosclerosis. First, it is obviously impossible to find any intelligent patient in serious distress who would submit to years of placebo therapy. It is also impossible to find any two individuals who are alike in the amount, quality, rate of progress, etc., of their focal atheromatosis. Previous investigators in the field of atherosclerosis (9) (10) (11), working with laboratory animals, had little difficulty; the animals could be sacrificed, the results studied and compared with controls.

In view of the impossibility, then, of the biopsy-before-and-after type of approach in human atherosclerosis, it was necessary to establish criteria utilizing, as the key, that most important organ of evaluation—the brain of the individual patient. (Unlike animals, man can describe his various symptoms and their varying degrees of intensity.) Knowing that there was a metabolic component in most symptoms, we used those least likely to have had their origin in the psychic sphere. Fatigue, for example, certainly has, in most instances, a large metabolic component. We soon had a list of symptoms which seemed to form a common denominator in most patients with disturbed metabolism, so that any change in the degree or character of the symptoms which paralleled the administration of therapeutic agents could be considered to be in large measure the result of the metabolic change created by those agents.

## V. Components of the Criteria Used in Evaluating the Metabolic Factor in Chronic Disease

1. *Metabolo-psychic component:* A set of symptoms present in most persons with or without organic disease is considered to be the result of a disturbed metabolism, and is as follows:

(a) *General:* Tiredness, nervousness, depression, irritability, weakness, forgetfulness, inability to concentrate, exhaustion, coolness, drowsiness, insomnia, etc.

(b) *Local:* Headache, dizziness, precordial distress, dyspnea, palpitation, leg pains, numbness, backache, etc.

2. *Hormone-Vitamin Component:*

(a) Therapeutic agents must be compatible with fundamental cellular metabolism. Those produced endogenously (hormones) and those occurring exogenously (vitamins), being fundamental to the control of cellular metabolism, seem most logical and necessary.

(b) These agents must be given in doses large enough to create a change or readjustment of the metabolism; their chemical formulae must be known and measurable, to make possible standardization at definite dosages; these agents are to be the *only constant* in the whole picture.

(c) As these agents are to be taken throughout the lifetime of the individual, they must, of course, be non-cumulative (water-soluble) and non-toxic.

3. *Therapeutic Effect:*

(a) There should occur gradual relief of these symptoms in persons of all ages, with or without organic disease, following the administration of these therapeutic agents.

(b) The symptoms must be relieved over a long period of time while treatment is continuous and the patient remains on maintenance dosages; the symptoms should recur within a few months or less, after treatment stops.

NOTE: In order to prove beyond any doubt that psychic symptoms have been relieved solely by the treatment of metabolic factor, the use of psychotherapy must be avoided, if possible, or very limited in the early stages.

If laboratory facilities are available, another important component may be added:

4. *Blood Cholesterol Measurements, Quantitative:*

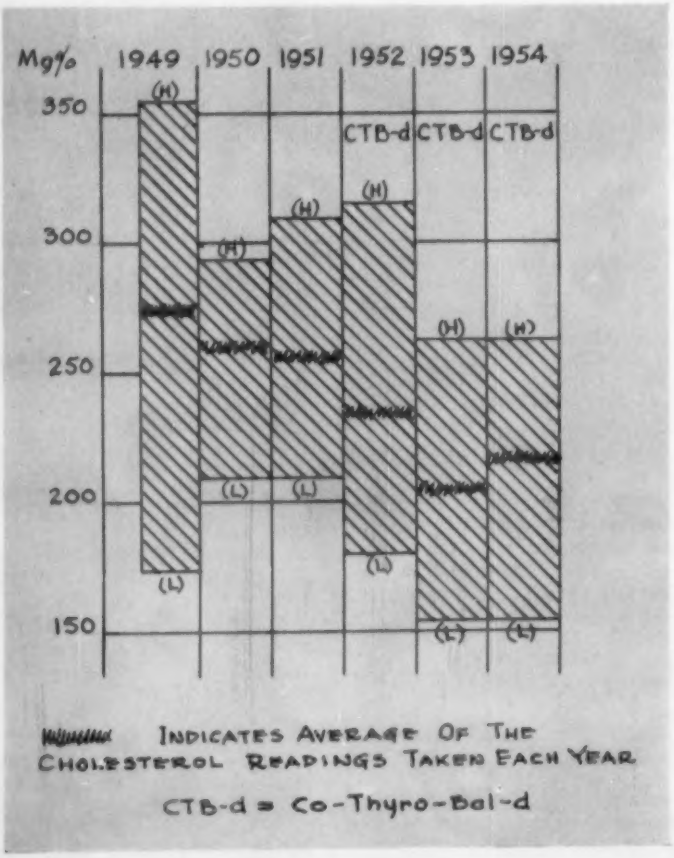
Any therapy which improves the fundamental cellular metabolism should create a stabilization of cholesterol levels at a lower and narrower range.

If an ultracentrifuge is available, another criterion may be added:

5. *Blood Cholesterol Measurements, Qualitative:*

The Gofman lipoprotein refractive index should show a definite improvement.

E. H.'s story in the last five years indicates that the criteria mentioned above—except "5."—have been met in full measure. Especially significant is the factor of time, i.e., the relatively long period during which he has been symptom-free, after his previous 7½ years of a progressively downhill course. This long period of deterioration and the relative immediacy of his therapeutic response should eliminate any suspicion that recovery would have been spontaneous. Furthermore,



there are many other patients under investigation with focal atheromatosis, who have responded similarly. E. H. was chosen primarily because of the relatively large number of cholesterol determinations which produced a significant cholesterol pattern from which deductions could be drawn.

*Lack of Criteria (5):*

Although last year the writer felt that he had enough evidence upon which to base conclusions that a new facet could be safely added to the control of atherosclerosis, confirmatory evidence using Gofman's lipoprotein refractive index method seemed necessary. Therefore, it was decided to wait until an ultracentrifuge was available to our group. However, when we presented our problem to Dr. John W. Gofman, he responded as follows:

(EXCERPT FROM PERSONAL COMMUNICATION DATED SEPTEMBER 24, 1954)

"You express in your letter that you would like to obtain large-scale confirmatory tests by the use of the ultracentrifugal technique before publishing your experiences in the field of therapy of atherosclerosis. I am not convinced that you should wait for such tests before publication of your experiences. While it is true that the serum cholesterol measurement does not provide as much information as the serum lipoprotein determination, I believe it is safe to say that whenever the serum cholesterol level is *lowered*, some important lipoprotein class will also be lowered. I am thoroughly convinced that the most fruitful prospect for cutting down mortality from the various forms of atherosclerosis resides in development of methods for reducing the circulating serum lipoproteins. If serum cholesterol can be lowered, *some* type of lipoprotein will be lowered and it becomes a secondary matter to explore *which* type and how much benefit may be anticipated therefrom. Thus I believe that if you have already developed safe, effective procedures for reducing and maintaining reduced serum cholesterol levels, you are far along the road to important solutions to the atherosclerosis. It would seem, further, of great importance to get this knowledge out in publication form as soon as possible, without waiting for . . . . . the ultracentrifugal determinations. I feel it is important that you get the findings out so the procedures can be tested and confirmed by others . . . ."

## DISCUSSION: GENERAL

This comprehensive review of a many-sided attack on the problem of atherosclerosis has been evolving since 1938, when synthetic vitamin B factors began to be available. Our inability at that time to administer adequate dosages of thyroid continuously, was not peculiar to ourselves: any physician then administering thyroid extract, was obliged to use small inadequate dosages, intermittently, with *caution*, because of the danger of "toxic" reactions. It was noted at that time that additions of the various water-soluble vitamins made it possible to administer larger doses of thyroid extract over longer periods of time, and by 1945 we had evidence (2) that a safe way had been found to administer thyroid extract in quantities even up to three grains daily, indefinitely, to almost anyone, arteriosclerotic or not.

When the lipotropic factors became available, it was observed clinically that patients seemed to tolerate larger maintenance doses of Oxytropin. Furthermore, the higher levels could be reached more rapidly. We have neither felt nor claimed that lipotropic factors are directly responsible for lowering human blood-cholesterol levels. However, since thyroid extract (at present the most practical key to the lowering of human blood-cholesterol levels) has greater effectiveness when administered with lipotropic factors, their use appears to be rational.

Intravenous thyroxin therapy was approached in the same manner. The tachycardia, palpitation and other side-reactions of intravenous thyroxin administered alone, are well known. When thyroxin is combined to form Co-Thyro-Bal-d and administered with excess B 12 in the manner described, not only are these side-reactions lacking, but there also seems to be marked augmentation of the therapeutic effect of the thyroxin.

The rationale for the low-cholesterol-high-protein diet has been discussed. To try to lower cholesterol levels with costly therapeutic agents on the one hand, while allowing the patient to gorge himself with high-cholesterol foods, on the other, would appear totally irrational. A rigid dietary regime, however, is stressed only in the early stages of treatment, for it has been found that patients on maintenance therapy are able to process lipids more adequately, and thus are permitted moderate amounts of the higher cholesterol foods when their general metabolism has reached improved levels.

No study has been made of the effect on human blood-cholesterol levels, of each individual substance in this many-faceted therapy. Our group had already evolved most of the facets of the therapy by 1948 when the clinical research program was actually instituted. We could not turn back the clock. New patients referred by others who had found the rounded therapy helpful, desired the same therapy. Had we divided these new patients into groups for study of the effect of diet alone, of thyroid alone, of thiamin chloride alone, of choline alone, etc., our research program would have ended rather abruptly. If intelligent patients with multiple complaints are not relieved within a reasonable period, they disappear from view.

A research scientist wishing to evaluate each facet of the multiple approach would find controls possible only in a well-regulated prison. There, various groups could be formed, each single substance added to the food of the various groups under study, and control studies made. However, the results of studies under even these rigid conditions might be considered of doubtful value, for the question would arise: would these same results have been obtained if the individuals under study were out of jail and exposed to the stresses and strains of our civilization? Which brings us to the primary concern of this article, i.e., to describe an effective, well-rounded approach to the control of atherosclerosis in general, wherein minimum amounts of various anti-atherosclerotogenic agents will produce maximum beneficial results in persons living under the highly varied stresses and strains of modern life.

As was mentioned earlier, coronary atherosclerosis was singled out in illustrative case-reports primarily because, of all the types of focal atheromatosis, it is the most difficult to treat. A discussion of this particular problem, then, seems in order.

## DISCUSSION: SPECIFIC

Most of the problems which occur in the treatment of coronary sclerosis seem to be related to the stage of the disease at which therapy starts. It is obvious

that many patients are pre-terminal at the time they present themselves for medical advice and treatment. A glance at the obituaries indicates that many persons die suddenly of coronary thrombosis without having consulted a doctor. Their disease had progressed gradually to the point where atrophic, fibrotic, hyaline, calcinotic, necrotizing, etc., changes had occurred in the media, and they succumbed to the first severe vascular accident. Suppose that the physician has seen this type of individual the day before—or the week before—or the month before the patient's death—and that palliative or hormone-vitamin therapy had been prescribed; the death of the patient now becomes the physician's responsibility. It is important in the education of individuals with coronary sclerosis that they be made to assume responsibility for having come possibly too late. The patient is told in simple terms the story of the lipoid imbalance which occurs in almost everyone; that he probably has had coronary atherosclerosis for years; that he feels precordial distress because of the extension of the lesion into the media; that the destruction of the elastic muscularis limits the expansion of the blood vessels, which in turn prevents adequate blood supply to the heart muscle.

He is told that there is no way of determining whether an occlusion is pending or whether he has come early enough to avoid a thrombosis. He is also told that if he decides to take treatment to adjust his oxidative and lipoid metabolism he must be very careful (in the first three months, at least) to keep in frequent contact with the physician, as there is no guarantee that a thrombosis will not occur. In the event of such occurrence he will have to be hospitalized immediately for the emergency of coronary occlusion.

Throughout the early discussions with the patient, however, it is rational and logical to allow him to feel hopeful that he may be one of the many fortunate individuals whose lesions have not progressed too far; and that he may join the high percentage of patients with symptomatic coronary disease who have been helped by the hormone-vitamin approach to the control of the lipoid metabolism.

The hormone-vitamin approach does not eliminate the use of palliatives which have been controlling the local symptoms of the patient with symptomatic coronary disease. He is told to continue those palliatives; in fact, they can be used by him to evaluate the effectiveness of the hormone-vitamin therapy. It is most gratifying to a patient to be able to cut down the use of nitroglycerin 75 to 100 per cent. However, as the hormone-vitamin approach is a form of substitution therapy for his own disturbed metabolism, it must be reiterated to him that the agents which created the favorable change in his metabolism must be continued indefinitely in order to maintain that change.

Very often a person who has seen an apparently healthy friend or relative die suddenly of coronary disease becomes interested in the problem, and his first questions may be: "Why and how did it happen?" and "What could have been done about it?" The whole story is told of over-nutrition in this civilization, combined with a hereditary and/or acquired metabolic imbalance, which led intermittently to the changes in the intima and media of the coronary vessels. If he is of more than average intelligence, his next question may be: "When is it best to start treatment?" He is told that there is no way to decide in each specific case the optimum time to begin therapy, as everyone is different, and no one knows whether or not his particular coronary atherosclerosis has begun. However, some generalization can be made. Because hormone-vitamin therapy has been found to be absolutely harmless over a prolonged period of time in the large majority of patients under treatment, almost any time is the best time, for the sooner the dietary habits and lipoid metabolism have been improved, the better. Such a generalization, however, will be ineffective in most cases until we of the medical profession have educated the public to the reality of the problem.

## SUMMARY AND CONCLUSION

A case report has been presented illustrating the method of approach used in adjusting the transitory and/or continuous lipoid metabolic imbalance present in focal atheromatosis.

The results obtained indicate the importance of continuous hormone-vitamin therapy, and seem to support the concept that vascular anoxemia resulting from colloido-plasmatic disturbances of the cholesterol-lipid metabolism is responsible for the production of atherosclerosis.

A new intravenous hormone-vitamin combination**** has been described which stabilizes blood cholesterol levels at a lower and narrower range and produces distinct symptomatic improvement.

****Acknowledgment is made to the Vascular Research Foundation for its help in developing and supplying the material used in this study.

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# HEPATOTOXIC EFFECT OF CORTISONE IN EXPERIMENTAL ANIMALS

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MANY INVESTIGATORS have reported beneficial effects from the administration of cortisone or ACTH in the treatment of acute and chronic diseases of the liver (1-7). Early in the present study an attempt was made to determine whether cortisone had any therapeutic effect on experimental liver damage produced by carbon tetrachloride. It soon became apparent, however that, contrary to expectations, cortisone had an additive effect on the carbon tetrachloride treated animal, augmenting the extent and severity of liver damage. As a result, it became necessary to include a series of experiments designed to study the action of cortisone alone on the liver structure. The purpose of this paper, therefore, is to demonstrate the effects of cortisone on the normal and pathological liver under experimental conditions.

## Material and Method

After studying the effect of cortisone on 73 male white rats, 34 which fulfilled the requirements of the experimental conditions of the present series were selected. Thirty-four rats, weighing 186 to 225 grams (average 206 grams), were subdivided into six groups as outlined in Table 1. Control animals (Group I) were given injections of 0.9 per cent sodium chloride solution. Group II received both cortisone and $CCl_4$, Group III, $CCl_4$ alone and Goups IV, V, VI received cortisone alone each at a different dose level. The method of administration of $CCl_4$ and cortisone has been summarized in Table I. The drug used was Cortisone Merck, 25 mg. suspended in one c.c. of saline. Sick animals were watched every three to four hours in order that postmortem examination could be made as soon as possible. Very sick rats were killed when death seemed imminent. Animals that died during the night have been excluded from this series. The rats were kept in an air-conditioned room. They were given free access to Purina chow and water. The animals were sacrificed by a blow on the head on the fourth day at the earliest and the thirty-fourth day at the latest. Liver tissue obtained immediately after death was fixed in ten per cent formalin, embedded in paraffin, sectioned to 5 microns and stained with hematoxylin-eosin.

In order to make an accurate comparison microscopially between the extent of liver damage in rats treated with cortisone and $CCl_4$ (Group II) and in rats treated with $CCl_4$ alone (Group III) the following quantitative cytological measurement of liver sections has been used. To reduce the size of the microscopic field a piece of black paper with an aperture 6.5 in diameter was inserted in the ocular of the microscope. Through this aperture, the normal looking cells and the cells with signs of nuclear degeneration were counted in 17 to 22 fields and a mean number per field was computed for each animal (Table 2). Karyolysis, karyorrhexis and pyknosis were considered as signs of nuclear degeneration. Areas which fell within the aperture, but which did not contain any liver cells such as the periportal spaces, large vessels and parts that were torn off the section, have not been included in the count. Using the same 5X ocular and 4 mm. objective for all slides this cytological, comparative study was made on Groups I, II, III, and IV. Groups V and VI, being a subsequent development of this study, have been considered separately.

## Results

Macroscopically, the liver of the control animals (Group I) and of those treated with 1.5 mg. of cortisone daily (Group IV) were normal. The livers from the animals in Groups II and III all showed small areas of necrosis varying from 1 to 4 mm. in diameter. There was no appreciable difference in the gross appearance in the livers of the animals treated with $CCl_4$ and cortisone, and those given $CCl_4$ alone. Microscopic examination of the livers of the control animals (Group

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TABLE I.

Rats treated with $CCl_4$, cortisone plus $CCl_4$, and with cortisone alone.

| Group | No. of Animals | Treatment | |
|---|---|---|---|
| | | Drugs Used | Dosage* |
| I | 8 rats | Saline | 0.1 c.c. once a day |
| II | 6 rats | Cortisone plus carbon tetrachloride | 1.5 mg. once a day<br>0.05 c.c. twice a week |
| III | 6 rats | Carbon tetrachloride | 0.05 c.c. twice a week |
| IV | 5 rats | Cortisone | 1.5 mg. once a day |
| V | 5 rats | Cortisone | 3 mg. once a day |
| VI | 4 rats | Cortisone | 10 mg. once a day |

*All drugs were administered by the subcutaneous route.

TABLE II.

Hepatotoxic Effect of Cort'sone on Normal and Pathological Liver as Shown by Quantitative Cytological Measurement.

| Group | Rat | No. of Normal Looking Nuclei per Microscopic Field (X) | No. of Cells with Degenerated Nuclei per Microscopic Field (X) | Total No. of Cells per Microscopic Field (X) |
|---|---|---|---|---|
| I | 1 | 28.0 | — | 28.0 |
| Control | 2 | 33.3 | — | 33.3 |
| | 3 | 32.9 | 0.1 | 33.0 |
| | 4 | 32.0 | — | 32.0 |
| | 5 | 31.2 | — | 31.2 |
| | 6 | 29.7 | 0.1 | 29.8 |
| | 7 | 30.9 | — | 30.9 |
| | 8 | 27.0 | — | 27.0 |
| | Mean | 30.6 | 0.0 | 30.9 |
| | σ | 5.9 | — | 5.9 |
| II | 1 | 10.2 | 7.9 | 18.1 |
| Cortisone | 2 | 13.2 | 12.1 | 25.3 |
| + | 3 | 21.4 | 3.2 | 24.6 |
| Carbon | 4 | 5.7 | 12.1 | 17.8 |
| tetrachloride | 5 | 9.9 | 8.3 | 18.2 |
| | 6 | 7.4 | 17.5 | 24.9 |
| | Mean | 11.3 | 10.1 | 21.5 |
| | σ | 5.1 | 4.4 | 3.5 |
| III | 1 | 19.1 | 5.2 | 24.3 |
| Carbon | 2 | 6.2 | 13.2 | 19.4 |
| tetrachloride | 3 | 22.1 | 5.7 | 27.8 |
| | 4 | 29.3 | 7.7 | 37.0 |
| | 5 | 17.2 | 6.2 | 23.4 |
| | 6 | 14.7 | 6.2 | 20.9 |
| | Mean | 18.1 | 7.3 | 25.4 |
| | σ | 7.0 | 2.7 | 5.8 |
| IV | 1 | 20.2 | 7.4 | 27.6 |
| Cort'sone | 2 | 25.4 | 2.1 | 27.5 |
| | 3 | 20.7 | 3.1 | 23.8 |
| | 4 | 17.1 | 4.1 | 21.2 |
| | 5 | 27.0 | 3.1 | 30.1 |
| | Mean | 22.0 | 3.9 | 26.0 |
| | σ | 3.6 | 1.8 | 3.2 |

(X) Average of 17 to 22 fields for each animal.

I) disclosed no noticeable histological changes. Groups II and III in which $CCl_4$ plus cortisone, and $CCl_4$ alone were used respectively showed varying degrees of hepatocellular degeneration or minute foci of necrosis in both the central and peripheral parts of the lobules. In the necrotic areas the cells had either completely disappeared or their contours were indistinct with karyolytic, karyorrhectic or pyknotic nuclei. Besides the loss of normal sharp cell outlines, the cytoplasm disclosed coarse granulation or vacuolization. Central and mid zonal congestion and edema of the sinusoids were marked in most of the sections. The Kupffer cells

appeared normal. There was no evidence of collapse, fibrosis, or exaggeration of portal canals. Rat 4 in Group II showed the most marked changes among twelve animals of Groups II and III, consisting of diffuse patchy necrosis. In the remaining 11 rats in Group II and III the histologic pictures of the liver did not differ visibly in routine microscopic examination. However, the quantitative cytological measurement described above discloses a statistically significant difference in the degree of the hepatic damage between the group treated with $CCl_4$ alone, and that treated with $CCl_4$ and cortisone together. The results of the nuclear changes are given in Table II.

The total number of normal looking cells in each microscopic field did not differ markedly among the three experimental groups (Groups II, III, and IV) but, the experimental groups showed a significantly smaller number than the control group (Group I). If the assumption can be made that all groups were homogeneous at the start of the experiment, this means that cells have "disappeared" in the experimental groups since the average total number of cells per field in the combined experimental groups was 24.2 while in the control group it was 30.7.

There was a highly significant difference among the groups with respect to number of normal cells. The $CCl_4$ group did not differ significantly from the cortisone group (combined mean = 19.9). The group which received both $CCl_4$ and cortisone had a significantly smaller number of normal cells (mean = 11.3) and the control group had a significantly larger number (mean = 30.6).

There was a real difference between the control group and the three experimental groups with respect to number of animals with degenerated cells. The control group had only two out of eight animals that showed even a small number of degenerated cells while in the experimental groups all 17 animals had an appreciable number of degenerated cells. (Probability of Chi-square less than .0002).

The experimental groups differed among themselves in mean number of degenerated cells (10.1 for $CCl_4$ and cortisone, 7.3 for $CCl_4$, and 3.9 for cortisone with a probability of "F" in the analysis of variance less than .05). On further comparison, the probability of "t" for Group III or Group IV was only slightly greater than .05; Groups II and IV showed no real difference; the probability of "t" for Group II or Group IV was equal to .02.

When percentage of cells degenerated was analyzed, the findings were substantially the same as for the number of degenerated cells (see preceding paragraph).

In animals treated with 1.5 mg. of cortisone daily alone, the most characteristic microscopic feature was cytoplasmic vacuolization, coarse granulation and loss of the sharp contour of cytoplasm (Fig. 1). In Groups V and VI receiving daily cortisone of 3 and 10 mg. respectively, the liver sections showed scattered necrotic areas or degenerated cells. Here too, cellular changes consisted of pyknosis, karyorrhexis and karyolysis. The most severe hepatic damage was seen in rat 3 from Group VI which received 10 mg. of cortisone daily for 5 days. The animal showed eight foci of necrosis each

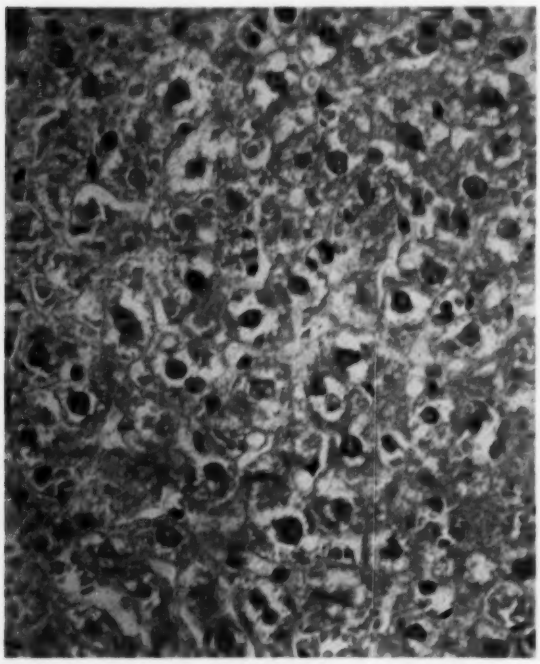

Fig. 1. Showing cytoplasmic vacuolization, indistinct cell contours and degenerated nuclei in the liver of the rat treated daily for five days with 1.5 mg. doses of subcutaneous cortisone. Hematoxylin and eosin X400.

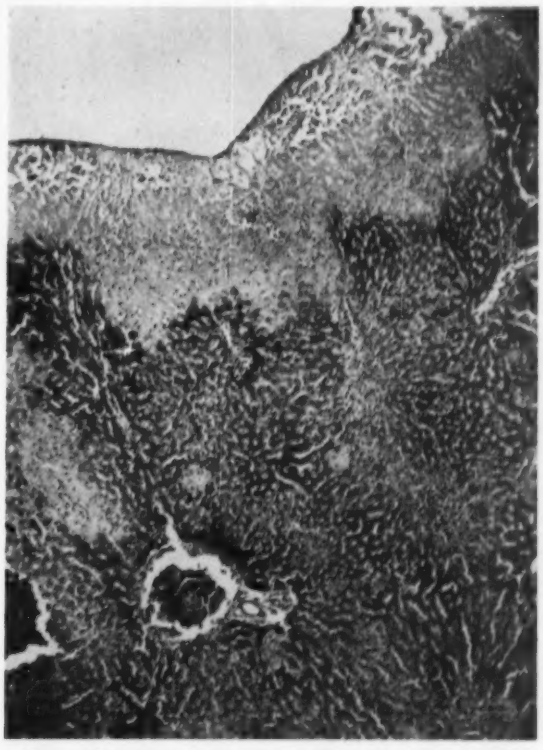

Fig. 2. Massive necrosis of the liver in the rat treated daily for four days with 10 mg. doses of subcutaneous cortisone. Hematoxylin and eosin X50.

with a diameter of 2 to 6 mm. Histologically these consisted of areas of coagulation necrosis (Fig. 2,3). There was no evidence of collapse fibrosis, periportal connective tissue and bile duct proliferation.

## DISCUSSION

In making a comparison between the extent of liver damage in rats treated with $CCl_4$ alone and that of rats treated with $CCl_4$ plus cortisone by means of the quantitative cytological measurement described above, the assumption was made that all parenchymal cells of the normal healthy liver are of similar size. The validity of this is suggested by the uniform measurements of the liver of our untreated control animals (Table II, Group I). Our study disclosed clearly a more pronounced hepatic damage in animals treated with cortisone plus $CCl_4$ than in those treated with $CCl_4$ alone. It further showed that cortisone itself has a distinct hepatotoxic effect when administered daily in subcutaneous dose of 1.5 mg., 3 mg. and 10 mg. The hepatic cell degeneration involved karyolysis, karyorrhexis, pyknosis, cytoplasmic vacuolization and loss of the normal sharp outline of liver cells.

We realize that the doses of cortisone used in most of these experiments exceed those commonly employed for clinical purposes. The administration of 1 mg. of cortisone to a 200 gram animal is probably equivalent to a 350 mg. dose in a 70 kilogram man; a 10 mg. dose, as used for each animal in Group VI corresponds to an injection of 3500 mg. of the drug clinically. The use of larger doses in Groups V and VI was intentional and was aimed at magnifying the hepatotoxic effect of cortisone, as observed in Groups II and IV.

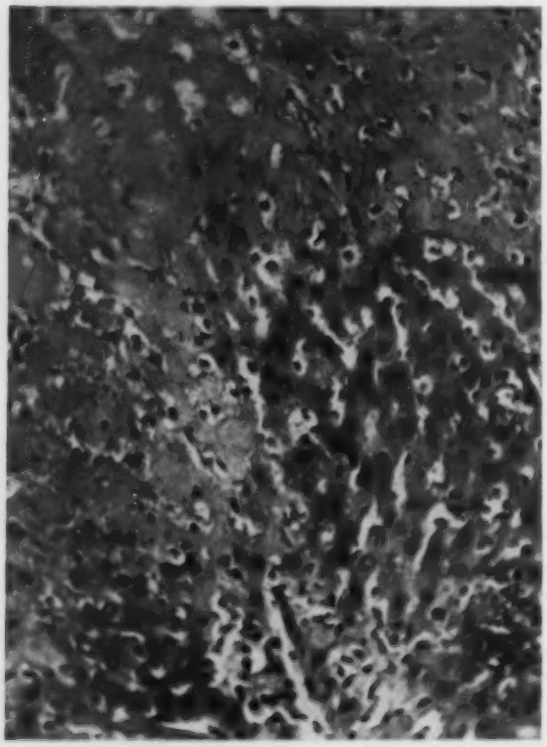

Fig. 3. Higher magnification of liver section shown in Fig 2. (H-E X200).

The hepatotoxic effect of cortisone is especially noteworthy in light of the interesting observations of Schwarz (8) who found that the administration of 1 mg. of the drug per 100 Gm. of body weight in rats delayed the development of dietary liver degeneration. The specific dietary conditions to which his animals were subjected may have been the factor responsible for the discrepancy between his findings and ours. Baker et al (9) studied the effect of adrenocorticotropin on liver structure under varied dietary conditions. They showed that fatty changes occurred in the livers of rats fed a high protein diet and treated with adrenocorticotropic extract. Under the experimental conditions of their study, however, the liver did not show significant degenerative changes.

Necrosis and degenerative changes of the liver and other viscera have been described by Selye after the use of "alarm-producing" factors (10). According to Antopol these lesions are similar to those produced by massive doses of cortisone (11,12). However, this assumption does not exclude the possibility of a direct, pharmacodynamic toxic effect of the drug or of its enhancing effect upon the virulence of bacteria which may cause indirect damage to the tissues (13).

The mechanism of action of cortisone upon the liver cell is unknown. Experimental studies with cortisone and ACTH may provide a useful tool for the investigation of the relationship of the adrenal glands and anterior hypophysis to the pathological cytology and physiology of the liver. Fatty infiltration of the liver found at autopsy in many cases of Cushing's syndrome (14-16) may be the clinical counterpart of the experimental hepatic damage produced by cortisone. In a case reported by Steinberg et al (17), hepatomegaly due to marked fatty infiltration, demonstrated by liver biopsy, developed during treatment of acute rheumatic fever with cortisone. The process was promptly reversed upon withdrawal of the hormone. Baldwin and her associates (18) observed enlargement of the liver in a number of children during adrenal cortical hormone therapy of active rheumatic fever. They believe that liver enlargement usually begins soon after starting the therapy and regresses more slowly on withdrawal of hormone therapy. In one case, liver biopsy showed that marked fatty infiltration present in the first section, had regressed considerably in the biopsy sections taken three weeks later.

Bongiovanni and Eisenmenger reported an unusual form of chronic liver disease of undetermined etiology (19). This type of cirrhosis (?) has been confined to females, usually under 35 years of age. Many exhibited hirsutism, acne, abdominal striae (without previous ascites), obesity, amenorrhea, and "moon facies." These features appeared concomitantly with the onset of jaundice or shortly thereafter; they did not appear to be the sequelae of prolonged hepatic disease but were associated with the earliest manifestation of the illness. The clinical findings in this Cushing-like syndrome were uniformly present at the time of the first examination and in some patients antedated the appearance of icterus. More case reports are necessary to confirm these observations.

Hallbrook et al (20) showed that there is a marked increase in amino acid excretion in patients with rheumatic arthritis, following remission during ACTH therapy. It is known that amino acids are excreted in excess in states of hepatic dysfunction.

It is difficult to draw any conclusions from the widely discrepant opinions expressed in papers dealing with hormone therapy of liver diseases (1-7, 21-29). A thorough evaluation of therapeutic results in hepatic disorders is impossible in the absence of fundamental principles such as control study, elimination of human error in evaluation and adequate number of cases. Past experience should not be used as control material in the appraisal of the therapeutic results. Present controversial reports are mostly based on impressions gained from a few scattered cases rather than on statistically significant findings. The rationale of the use of cortisone in the therapy of hepatic disease is not supported by the present study. However, one must acknowledge species differences and await final conclusions drawn from controlled studies of cortisone on a large series of patients.

## SUMMARY

1. A quantitative cytological approach in the comparative study of liver damage is described.

2. Varying degrees of hepatocellular degeneration and necrosis were found in animals treated with cortisone in maximal doses.

3. The hepatotoxic effects of carbon tetrachloride poisoning were augmented, and not reduced, by concomitant treatment with cortisone.

4. The rationale of therapy with cortisone in human cases of liver disease is discussed.

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# A THEORY OF PATHOGENESIS OF DUODENAL ULCER

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THE PATHOGENESIS of peptic ulcer has been a controversial problem. There is general agreement that the direct cause is a digestive action of hydrochloric acid and pepsin on the mucous membrane of the stomach and duodenum. But other causative factors must contribute, otherwise every individual would suffer from peptic ulcer, and, furthermore, from multiple peptic ulcers. As contributing factors have been suspected: 1. mechanical conditions exposing certain areas to peptic digestion, 2. failure of local circulation, 3. damage of the mucous membrane by inflammation, 4. increased production of gastric juice rendering the gastric contents hyperacid, 5. congenital, inherited, diminished resistance of the tissues to peptic digestion. Furthermore, there may be causes behind the causes. One of the latter could be of a nervous or psychic origin. We have to refrain from discussing pro and con of all these theories and from quoting all the publications contributed by so many authors. There are excellent treatises about all these problems in Ivy, Grossman and Bachrach's monograph (11) and in a collective monograph edited by Sandweiss (21). My present inquiry aims only at directing attention to an idea not considered by other authors, although I mentioned it briefly (1929) (17). Of all the other theories a nervous or psychosomatic pathogenesis only shall be criticized later.

In contrast to speculative conceptions there are certain facts which have been repeatedly confirmed, although their interpretation may be questionable. One of these facts is the hyperacidity of the stomach contents in cases of ulcers of the duodenum. Riegel (18) was the first who explained the origin of peptic ulcers by hyperchlorhydria, by hypersecretion of the glands of the stomach. But later authors observed many ulcer patients with normal or diminished secretion. Moynihan (15) recognized that hyperchlorhydria appears frequently in cases of duodenal ulcer, but not in cases of stomach ulcer. He suspected that a majority of recent cases of ulcus duodeni may show hyperchlorhydria, but in stenotic duodenal ulcers the retention of food substances in the stomach may lower the secretion of acid. Of his material of ulcus duodeni 40 per cent was hyperacid. Many subsequent authors confirmed Moynihan's findings. Hurst (10) attributed the hypochlorhydria and other symptoms of duodenal ulcer to a constitutional diathesis which he named "duodenal diathesis." Thirty years ago I examined in collaboration with L. Kaufteil (12) the gastric secretion of duodenal ulcers with Ewald test meal and determination of the pH of the filtrate and found an extreme hyperacidity in 100 per cent of the uncomplicated cases. Patients with retention of food substances because of duodenal stenosis showed sometimes normal acidity or subacidity, but, if after treatment with diet and lavages the retention ceased, the acidity increased often to hyperchlorhydria. Ever since, further experiences confirmed my observations. Whenever I saw a case apparently suffering from duodenal ulcer without hyperacidity, it turned out to be either a duodenal ulcer with food retention, or it was a healed ulcer with a deformed duodenal cap and pains caused by another condition such as gall bladder disease, or the deformity was brought about by adjacent organs or tissues. The examination with Ewald test meal has to be correctly performed in order to recognize hyperacidity. I saw cases of ulcus duodeni with the report of normal acidity. It turned out that the technician executing the test withdrew the stomach contents after half an hour of digestion instead of waiting at least three-quarters of an hour. She explained that by waiting three-quarters of an hour to an hour she would be unable to obtain enough stomach contents for titration. A repeated correctly executed test showed hyperacidity. An error sometimes encountered is using another test meal but comparing the result of the examination with the normal figures of the Ewald test meal. For example, a test meal high in protein may show in a case of ulcus duodeni a pH of 1.6 - 1.8 which are the figures of normal persons after an Ewald test meal. Furthermore, sometimes a prepyloric ulcer presents an x-ray picture resembling a duodenal ulcer and is diagnosed as such. A normal acidity in such a case seems to contradict the rule of hyperacidity in duodenal ulcer. Considering all these possiblities the number of cases of uncomplicated duodenal ulcer with normal acidity or subacidity would shrink to a minimum. But disregarding these interpretations all authors found hyperacidity in the great majority of duodenal ulcers. Therefore, the association of hyperacidity with duodenal ulcer cannot be a mere coincidence, and this problem has been discussed frequently, recently very thoroughly by Shay and Lorber (24).

Hyperacidity could be 1. the consequence of duodenal ulcer, 2. its precursor and cause, 3. both the effect of a joint cause. There is a mechanism in the duodenum and jejunum lowering the secretion of the stomach. The ulcer in the duodenum may affect its lowering influence on the acid production of the stomach. As Grossman (9) pointed out, however, healing of the ulcer should restore the above-mentioned mechanism of the duodenum, but experience shows that the hyperacidity remains for a long time the same. I myself observed patients with duodenal ulcers for many years and the hyperacidity remained unchanged although there were no ulcer symptoms for years, and the x-ray picture failed to show an active ulcer. Furthermore, hyperacidity occurs without duodenal ulcer.

The second possibility, that the hyperacidity may be the cause of the ulcer, is much more probable. Experimental stimulation of acid secretion in animals with different methods produced chronic duodenal ulcers almost regularly, antrum ulcers as an exception. But, as Grossman (9) points out, there was an excessive acid production as it never occurs spontaneously in humans. Therefore, Grossman doubts that the intensity of acid secretion as encountered in duodenal ulcer cases could cause an ulcer. In my opinion the animal experiments have not been continued long enough to decide this question. The hyperacidity in humans may have

wrought its destructive work for years before an ulcer developed. It has been shown in various animal experiments and by the occurrence of jejunal ulcers in gastroenterostomy that even normal acidity produces an ulcer in a mucous membrane which is not immune to peptic digestion. Another objection to this theory is the experience that duodenal ulcers are rarely associated with stomach ulcers. However, the living mucous membrane of the stomach is immune to peptic digestion, whereas the mucous membrane of the duodenum becomes eroded if the incoming acid is not neutralized. A third objection could arise against any theory of origin of peptic ulcers: We see only one chronic ulcer in a case, rarely two, almost never more. One would expect multiple ulcers, and, as a matter of fact, experimental acute ulcers in animals are mostly multiple ulcers. Mechanical factors may play a part here, converting an acute ulcer to a chronic one. On the spot of an acute ulcer the muscularis mucosae contracts and protects the ulcer from further erosion by covering it between folds. It may happen accidentally that an acute ulcer perforates the muscularis mucosae; it cannot be protected any longer and becomes chronic.

A third explanation of the association of duodenal ulcer and hyperacidity has been much discussed recently. Increased nervous impulses by way of the vagus nerve may produce both ulcers and hyperacidity, the ulcers by spastic contractions of arteries and stomach muscles, shutting off the blood supply with subsequent peptic digestion of the necrotic tissue. This theory, although not new, has been re-established by new research. Wolf and Wolff (26) visualized the mucosa of the stomach of a patient with chronic fistula of the stomach. They saw that certain emotions such as anxiety or resentment caused hyperemia, hypermotility, hypersecretion of the mucosa. Continual action of the peptic juice on an erosion converted it into an ulcer. Dragstedt (3) conceived the successful surgical treatment of peptic ulcers with vagotomy. The psychosomatic medicine focused its theories on the digestive tract and claimed a psychic origin for peptic ulcer. There is some experience supporting this line of thought. Emotions are known to provoke ulcer pains. English authors reported increased frequency of hemorrhage and perforation of ulcers during bombing attacks on London in the Second World War. Another fact supporting these theories is the observation that cerebral pathology is often associated with acute ulcers of the stomach. Rokitansky (19) was the first who noticed this coincidence more than 100 years ago and suspected that the brain lesion irritates the vagus centers and increased stimuli cause the hypersecretion of the stomach by way of the vagus nerves. The hyperacidity in turn corrodes the mucous membrane of the stomach. Some psychiatrists and psychoanalysts claim that ulcer patients show a peculiar pattern of personality. Other authors find in ulcer patients signs of irritation of the autonomous nervous system, neurotic stigmata. But there are many objections to these theories. If duodenal ulcers and hyperacidity both were caused by increased activity of the vagus nerves, why does not hyperacidity occur in stomach ulcers as often and as regularly as in duodenal ulcers? The characteristic personality pattern of ulcer patients, the stigmata of neurosis have not been confirmed by experienced observers, nor are there statistics as to how many ulcer patients show the alleged pattern, and how many control persons. According to my own experience duodenal ulcer patients hardly ever give the impression of a psycho-neurotic personality. Most of these patients are contented, balanced persons, resistant to mental shock. No signs of increased sensitivity of the autonomous nervous system of the chest organs, intestines, or pelvic organs are manifest. Furthermore, ulcus duodeni is much more frequent in males than in females, whereas psycho-neurotic signs are seen more often in females than in males. That emotions provoke ulcer pains or hemorrhage is not necessarily a proof of a psychogenous etiology of peptic ulcer. Emotions activate symptoms of other diseased organs just as well; there is a mental factor in any disease or in the reaction of man to any disease. However, this does not prove neurogenous or psychogenous origin of organic diseases. For example, emotions may precipitate attacks of angina pectoris or even coronary thrombosis but that does not prove that coronary sclerosis is a psychogenous disease. Emotions may precipitate gallstone colics but they do not produce gallstones. Wolf and Wolff observed that resentment, anxiety produce hyperemia and hypermotility of the stomach and thus pains and hemorrhage of a peptic ulcer could be started, yet the ulcer itself may be due to other causes. Besides, there are emotions depressing stomach secretion and motility such as fear, sadness, and disgust. Nervous persons tend not only to rage, hostility, but to fear, dread and panic as well. The association of erosion of the stomach with cerebral lesions makes it probable that stimulation of the vagus nerves is one of the many causes of acute ulcerations but there must be other causes transforming them to chronic peptic ulcers. Moreover, true psychoses are not associated with duodenal ulcers more often than they occur in non-psychotic patients. Should we accept a psychogenous origin of hyperacidity, psychiatrists and psychoanalysts should succeed in removing the hyperacidity by psychotherapy. In a discussion of this problem at a scientific meeting some years ago I challenged a psychoanalyst to take up this investigation and thus to convince me of a psychogenous cause of hyperacidity. I have not heard from him since. If hyperacidity were a psychogenous condition we would expect changes of acid production over longer periods as emotions change through many accidental circumstances. But, as mentioned above, in uncomplicated cases of duodenal ulcer I never saw a major change of acidity during a long observation. Such changes reported in the literature may concern duodenal ulcers with retention of food in the stomach. If we would succeed in discovering a method or medication curing hyperacidity or if the hyperacidity would vanish spontaneously, the problem of healing duodenal ulcers would be easy. As it is up to now, the hyperacidity persists stubbornly and the ulcer reappears after a period of apparent healing.

What causes hyperacidity? We already refuted the theory that it is brought about by some agent stimulating the vagus nerves. We know that the secretion of the stomach is caused by impulses reaching the glands on the way of the vagus or by the action of certain substances on the mucous membrane of the antrum. As the vagus mechanism is ruled out, it must be produced by an excessive reaction of the mucous membrane of the antrum. What kind of change of the an-

trum mucosa could it be? We know that the lachrymal glands secrete on stimulation of the conjunctivae. We observe an excessive lachrymal secretion in case of conjunctivitis. There exists a psychogenous lachrymal secretion, too, but nobody would explain excessive lachrymal secretion on stimulation of an inflamed conjunctiva as psychogenous. We could assume an analogous behaviour of the mucosa of the antrum of the stomach and expect that antrum gastritis is the cause of hyperacidity. There is also another explanation possible. An inhibitory mechanism in the antrum mucosa, sensitive to a threshold concentration of hydrochloric acid, stops normally further production of gastrin, the hormone stimulating the corpus glands to secretion. Gastritis of the antrum could disturb this inhibitory mechanism so that the secretion of hydrochloric acid continues far beyond normal acid concentration.

Is there any evidence of antrum gastritis in duodenal ulcers? Konjetzny (13) examined the mucous membrane of resected stomachs in duodenal ulcer cases histologically and found regularly antrum gastritis. Orator (16) in Europe, May (14), Aschner and Grossman (1) in the United States confirmed Konjetzny's findings. However, there were objections from different quarters. Walters (25) examined the material of the Mayo Clinic and saw gastritis of the resected antrum of duodenal ulcer patients only in a minority of cases. He explained this discrepancy by regional influences. But, as mentioned, other authors in the United States corroborated Konjetzny. Schindler, Necheles and Gold (22) tried to elucidate the divergence. They performed experiments on dogs imitating the conditions prevailing in resection of the stomach in humans. They found erosions and swelling of the mucosa caused by congestion and corrosion which latter was produced by hydrochloric acid introduced into the stomach prior to resection. The difference between Konjetzny's and Walter's results depends, according to Schindler, Necheles and Gold, on the way the resection is performed. Sanders and Mecray (20) made analogous dog experiments and they also saw swelling and erosions of the resected stomach. However, in Konjetzny's research, infiltration of the mucosa, submucosa and even of the muscularis with leucocytes and lymphocytes proves the inflammatory nature of the changes, whereas Sanders and Mecray failed to see any cellular infiltration. Schindler and collaborators found some plasma cells in the mucosa which occur even in normal stomachs. Furthermore, Konjetzny found widespread antrum gastritis but corpus gastritis only in spots or none at all, whereas the changes observed in the dog experiments were extensive in the corpus mucosa but slight or absent in the antrum. Further objections were raised by gastroscopists. Some gastroscopists saw antrum gastritis in the majority of duodenal ulcer cases, others observed it rather as an exception than as a rule. Yet gastroscopy has difficulty to visualize the whole antrum. Gross changes only such as hemorrhage, hypertrophy or atrophy show evidence of gastritis in gastroscopy, whereas other inflammatory elements can be observed only by histological examination. A discrepancy between gastritis diagnosed by gastroscopy and one checked by histological examination has often been reported.

Recent animal experiments of Dragstedt (2,4,5,6) and collaborators are very interesting with regard to the problem of hyperacidity. These authors implanted the antrum of dogs into the colon and measured the secretion of a pouch of the corpus of the stomach. The secretion showed an extreme hyperacidity. In another experiment the antrum pouch was implanted into the colon and the colon with an adjacent part of the ileum was separated from the rest of the intestinal tract, forming a Thiry-Vella fistula. If this ileocolic segment was kept open and clean, the secretion of a gastric corpus pouch of the same animal was normal. After closing one end of the loop, hyperacidity appeared. Dragstedt explains the latter by increased pressure inside the antrum pouch. However the mechanism acting on the antrum may have been, Dragstedt's experiments show, that encroachment on the antrum can produce hyperacidity.

There is a symptom indicating that the antrum of the stomach may be involved in the origin of hyperacidity in man (17). Since Head and MacKenzie's research it is well known that diseases of internal organs cause hypersensitive areas of the skin and muscles innervated from the same segments as the organs. An ulcer of the antrum or duodenum produces a sensitive pressure point of the rectus abdominis muscle of the right side one inch above navel level. The same sensitive spot can be observed in hyperacidity of the stomach without ulcer, pointing to pathology of the antrum or duodenum or other organs innervated by neighboring segments. If the duodenum and other organs such as the gall bladder can be ruled out as is often the case, the antrum of the stomach is left as the cause, and if an ulcer or growth of the antrum can be ruled out, antrum gastritis remains. As a matter of fact, we observed hyperacidity in such cases.

Furthermore, the role of the antrum in producing hyperacidity is illustrated by the experience about acidity after antrectomy. Antrectomy has been the most successful operation for curing duodenal ulcers. The stomach secretion drops to a very low level. The great majority of duodenal ulcer cases after antrectomy fail to show free hydrochloric acid (Schur and Plaschkes (23) and many later authors). In contrast the acid secretion of duodenal ulcer cases after vagotomy drops only to the normal but there is still plenty of free hydrochloric acid (Dragstedt (2,3,8) and others). This shows that the secretory impulses from the antrum are much stronger than those from the vagus.

If we accept antrum gastritis as cause of hyperacidity and ulcus duodeni, the question arises, how the antrum gastritis originates. In the first place we have to refute the supposition that the antrum gastritis could be caused by the hyperacidity and not vice versa. The living mucous membrane of the antrum is immune to corrosion by peptic digestion, but if the antrum gastritis would be really produced by a repeated injury of peptic digestion origin, ulcers would also develop. Simultaneous occurrence of duodenal and antrum ulcers would be more frequent than actually observed.

Our knowledge of the etiology of gastritis rests on loose foundations. We know that acute gastritis manifested as indigestion follows damage through badly prepared decomposed food, through poor mastication, overeating, through excessive use of strong spices and strong alcoholic drinks, through poisonings. There is a

hematogenous gastritis, for example in infections, poisonings but we do not know much about it. We assume that repeated damage and injury produce chronic gastritis. There is the experience that badly prepared, decomposed food, poor mastication, irregular eating, poisonings cause prevalent corpus gastritis with subacidity and anacidity whereas excessive use of spices, acids and other stimulants of stomach secretion cause hyperacidity, that is antrum gastritis. If we question patients with hyperacidity with or without duodenal ulcers about their eating habits, they admit that in the past, before their complaints started, they used to eat highly seasoned food. We fail to see signs of psycho-neurosis or of an unbalanced autonomous nervous system in these patients, as mentioned above. On the contrary, they give the impression of an even temper, a contented mind which puts up with the realities of life. Many of these patients are obese or at least well nourished with the exception of some with advanced duodenal ulcer. But even most of these latter cases were in a well fed condition before the ulcer pains and the diet restricted food intake and caused loss of weight. Hurst (10), one of the first clinicians who examined ulcer patients with x-rays, described a constitutional type that he named duodenal diathesis. The stomach of these patients appears in the x-ray picture as a hypertonic stomach of oxhorn shape with hypermotility and fast emptying. This unusual motor activity and the hyperacidity are, according to Hurst, part of an inherited constitution, and he describes families with many cases of duodenal ulcers. There are other observations in the literature about hereditary inclination to peptic ulcer, and some advocates of psycho-neurotic origin of the disease assume congenital genesis of the psycho-neurosis. All these observations can be explained as well from the viewpoint of our theory: The patient with duodenal ulcer has been born as a vigorous individual, with mental resistance to adversities. He or she develops a good appetite under any circumstances, loves to eat and inclines therefore to obesity. He likes spices as most people with good appetite, indulges in highly seasoned food and overeats sometimes. In this way he contracts antrum gastritis with hyperacidity. This disorder does not manifest itself by symptoms for a time. Later belching or heart burn may occur or the duodenum may become eroded and ulcer may ensue. The good state of nutrition of the patient may explain the peculiar motility. The stomach is well supported in the tight, fat-lined abdomen, therefore the food is pushed up to the upper part of the stomach, the antrum appears narrow and the stomach looks hypertonic. The antrum contracts easier because it does not have to overcome the gravity as in cases with a ptotic stomach and the emptying is faster.

The observation of Hurst and other authors of frequent occurrence of duodenal ulcers in certain families may be explained as congenital vigor of the members of these families, which induces them to indulge in heavily spiced foods. Besides, the family members may acquire the habit of highly seasoned food at mother's table. Sometimes individuals of asthenic type may, of course, love spices too and contract hyperacidity and duodenal ulcer. That explains the occurrence of a minority of cases of duodenal ulcer in asthenic nervous persons with a ptotic stomach.

The frequent occurrence of duodenal ulcers in business executives has been explained by business worries, by overwork and mental stress. Our theory would explain it by the obligation of business executives of attending many dinner parties, conventions and convivial gatherings, of dining and wining important persons and customers.

Our theory regards duodenal ulcers only. Stomach ulcers are not associated with hyperacidity, most cases show normal acidity or even subacidity. The origin of stomach ulcers seems to be different from that of duodenal ulcers (7,8). Hyperacidity does not seem to play a part because few patients with duodenal ulcers have simultaneously stomach ulcers.

The knowledge of pathogenesis of the duodenal ulcer is not only of theoretical interest, but even more of practical importance. If the ulcus duodeni were of psychosomatic origin, psychotherapy would be the main treatment of the patient and should be used even as a prophylactic measure in individuals presenting the alleged emotional pattern of duodenal ulcers. If, on the other hand, antrum gastritis is the cause, warning against excessive use of seasoning should be part of public education, gastric analysis at intervals should be performed as a routine and, in case of hyperacidity, dietetic measures should be taken in order to prevent the outbreak of duodenal ulcer.

## Summary

1. The regular occurrence of hyperacidity in duodenal ulcer cases is emphasized and the cause of this coincidence discussed. Hyperacidity may be the predecessor and cause of duodenal ulcer.

2. The theory of psychosomatic origin of peptic ulcers is criticized.

3. Hyperacidity may be produced by antrum gastritis.

4. Antrum gastritis may develop through excessive use of seasonings in food.

5. As vigorous individuals lean toward excessive use of spices and vigor of constitution is inherited, the frequent occurrence of duodenal ulcers in certain families seems to be explained.

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# FOOD FADS AND FADDISTS

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THE EVERGROWING awareness on the part of many people as to the importance of nutrition to general health has helped to produce a "nutritional gold rush" on the part of many unscrupulous promoters of dietary fads. While dietary fads are not new, they have never been so profitable. Today's "Medicine Man" has an unparalleled opportunity to disseminate his misinformation through books, magazines, lectures and various types of advertising. The local climate is particularly suitable for faddism to flourish. The area long known as a haven for retired people abounds with quacks and food faddists who thrive on the higher incidence of chronic disease that is usually prevalent among such an elderly population. However, the faddist has convinced thousands of others as well, of the justice and truth of his statements.

A recent compilation of a committee of the Community Nutrition Section of the American Dietetic Association classifies into a few principal groups a list of about 231 bits of food misinformation current in the United States (1). However, in a short discussion of this type it is obviously impossible to take up each of the hundreds of examples of food faddism. We will discuss a few of the more important ones as well as call attention to some of the characteristics of this present day pseudoscientific super salesman, the food faddist.

Nearly always the food faddist is a fluent speaker. However, in addition to the smoothness of his presentation, his effectiveness is largely dependent on the fact that he is trading primarily on the hopes and fears of people. The sick eagerly grasp at any hope which will promise them health while at the same time, the healthy are afraid of losing that which they have. In some ways the faddist, if he were properly trained, could do a service here. There appears to be no question in the minds of many medical men that hope is an important part of their medical armamentarium. It is unfortunate that only too often many of them forget this with the statement "I'm sorry there is nothing that we can do about it." This may be true but surely something can be tried, something attempted, something done. The patient should not be abandoned to fate. When that happens, he then becomes the fertile ground for the quack and the food faddist.

The most serious aspect of this business however occurs with patients that may never seek competent advice. They believe the faddist and his special concoctions will cure them of their symptoms. The latter may simply be warning signs of serious diseases which may need prompt attention. Instead they will continue on a futile and fruitless venture until it may be too late for proper medical or surgical therapy. This in many ways may be the real tragedy of food faddism. The faddist will promise abundant health to anyone regardless of the conditions. Either because of lack of scruples or because of ignorance, or both, he is flagrant and devoid of humility; his knowledge has no limitations, his answers are always positive. There are no ifs, ands, or buts in his statements. He is always very dogmatic.

The very dogmatic nature of his statements offers the greatest appeal to the uninformed. The author of a very recent and very popular book on nutrition expressed himself with such finality when he suggested that blackstrap molasses is effective in menopausal difficulties and menstrual abnormalities, in inducing sleep, preventing and correcting nervousness, cor-

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recting baldness and restoring gray hair to its natural color, promoting better digestion, healthy nerves, healthy heart, preventing changes due to old age and promoting normal functioning of the glands. Unfortunately he does not state what glands are restored to normal.

In general the food faddist always has something to sell. This may take the form of a dietary supplement designed to restore the body chemistry to normal, whatever that may mean. It certainly sounds good. I'm sure we all want our body chemistry to be normal. However, there are several fundamental flaws with this argument. In the first place science isn't always quite sure just what these normal values should be, or even the significance of any possible deviation once a normal value has been accepted—or what can be done about it. A good example to illustrate the above situation is our present state of knowledge regarding the relationship between cholesterol and atherosclerosis. In addition to special food supplements, he also may sell squeezers, juicers, grinders, books, etc. He may go around the country offering "free lectures" followed by the sales approach offering personal evaluations advice at many dollars per hour.

It would be advantageous to state a few fundamental principles of nutrition before we proceed further in this problem of food faddism. One can think of nutrition in terms of the common foods such as steaks, milk, fruits and vegetables or in terms of the essential nutrients. It has been estimated that the body needs approximately 60 of these nutrients. These are the amino acids, fatty acids, vitamins, minerals, etc. These nutrients are the pure chemical entities that are ordinarily found in food. If we mixed these 60 chemicals in their proper proportions we would have what is commonly referred to as a synthetic diet. However, we cannot construct such a synthetic mixture from pure compounds in a manner that will produce the same growth promoting effects as preparations made from natural foods. In addition while we could feed the synthetic mixture to rats, we ourselves would not eat it because such a mixture is not too palatable to man. Man considers eating as a pleasurable experience as well as a necessity. We must realize that vitamin and mineral supplements cannot be substituted for customary food. The process of digestion and the rate of liberation as well as absorption of some of these nutrients is important to good nutrition. This may explain why synthetic diets are not quite as good as those using natural foods (2).

The vitamins are not food, they are useless without proper substrate of good food. Dietary supplements may not always correct poor dietary practices. The use of multivitamin pills and mineral supplements under certain conditions have real value. It should be pointed however, that natural foods contain in addition to known essentials other nutrients that are not available in these supplements. In the opinion of the author, money spent for these "dietary supplements" would be better spent on extra meat, milk, fruits and vegetables. The single most important practical suggestion from the viewpoint of good nutrition is for people to eat a variety of foods. Variety in the diet is much more likely to provide the needed essential nutrients. These nutrients are widely dispersed in nature and can best be obtained from many combinations of foods. It makes no difference whether a man receives these nutrients from milk or from yoghurt, ice cream or cheese.

No attempt is being made in this discussion to depreciate the nutritional value of yoghurt or wheat germ or even of seaweed. It is felt, however, that the nutritive value of these foods can be matched by less expensive foods at the grocery store. It certainly won't kill you to eat them. However, neither will it kill you not to eat them. Most people get their essential nutrients from more conventional food. However, if you like blackstrap molasses eat it. It does provide a negligible amount of vitamins as well as considerable amounts of some minerals. The minerals are usually in adequate supply on a good mixed diet. On the other hand in order to obtain the minimum requirement of 3 essential B-vitamins one must consume one gallon of molasses. In addition part of the iron is present in the form of insoluble rust (as a contaminant from machinery) which may have no food value. A more balanced source of iron could be derived from eggs.

A fertile field for faddist exploitation is to be found in the present interest in problems of obesity. In every case of overweight it may be said unequivocably that more food is eaten than the body requires. No reducing system can do more than establish a negative energy balance.

The problem of whole wheat versus white bread is another area of exaggerated misrepresentation. It is true that from the point of view of chemical composition and some animal experiments the whole wheat products are superior to the white flour. However, man does not live by flour alone. He eats bread not only enriched by those B vitamins needed in greatest amounts but also by the proteins of milk. In addition the absorption of nutrients from wheat flour is not as efficient as from products that have less cellulose. There are many digestive tracts that cannot tolerate the extra roughage. The slight differences that may appear in some animal experiments completely vanish if the bread is not made the sole item of diet but only a minor component. The latter represents the situation as we usually find it in man. However, the faddist is basically correct in his statement that adding iron and the three B-vitamins is only a partial approach to whole wheat. The full grains still contain other vitamins, minerals, and more protein of better nutritional quality. It has been estimated that grain foods afford over one-fourth of the protein in our national food supply. A better and more efficient use could be made of this protein by the process known as "natural enrichment." The latter involves the use of a good protein supplement such as the previously mentioned milk supplementation. Other excellent "natural enrichers" are wheat germ, corn germ, soy flour, brewers' yeast and dried egg. All of these offer valued protein, minerals and vitamins. Thus, the addition of 5% soy flour to 95% white flour increases the protein content by 19% and the combination gives twice the growth-promoting value of wheat flour alone.

It is unfortunate that some have seized upon the results in the recent literature to claim a nutritional superiority of one cereal over certain others. This practice is unwarranted. Breakfast cereals are eaten with milk, only rarely with water alone (as is usually the case in animal experiments). Any differences in the

biologic value of their proteins is usually obliterated when consumed with the large amounts of milk that man uses for their consumption. In addition, if they accomplish nothing else, they provide a vehicle by means of which many people take milk, possibly more milk than they would take if these cereals were not available.

What about milk? Must we eat raw milk? How destructive is pasteurization? The faddist tells us that we must eat raw milk. There are slight nutritional losses as a result of pasteurization. However, they are not severe and are worth the slight cost in nutrients in order to get the extra safety factor from possible infectious diseases. The same people who tell us that these infectious diseases could be controlled by proper bacteriologic controls tell us that it is too risky to depend on laboratory controls for the addition of fluorine to public drinking supplies.

A recent study by Elvehjem (3) and his group has demonstrated that raw, pasteurized, and homogenized milks have comparable nutritive value. This study not only measured growth, but reproduction and lactation performance through three generations.

The depleted soils theme is usually pushed for all its worth by the faddist. "There is no use of your trying to eat a balanced diet, your food is devitalized, demineralized as a result of it being grown on depleted soils. It is like so much wind filling the stomach but not feeding the body." In the first place soil deficiencies here and there are not significant in a country which uses food from so many diversified sources. Secondly, deficient soils seldom yield significant crops. The vitamin and protein content of plants is more dependent on genetic differences than on soil. Thus corn can be bred to have more niacin, a vitamin in which ordinary corn is notoriously deficient. There are studies going on of similar character which are attempting to produce by genetic manipulation, a corn with more balanced amino acid composition and thus eventually make it a better food for millions of people.

Mineral deficiencies in the soil can decrease the mineral content in the plant, but again it must be emphasized that with rare exception man does not live exclusively from food that comes from a single plot of land.

Admittedly there is still much to be learned about the relationship between soil fertility and the biological value of foods. This lack of knowledge may at times make it impossible for science to "disprove" the unfounded statements of faddists. Needless to say, however, most faddists are not concerned with proofs, or with the use of proper experimental controls.

Conflicting claims have appeared regarding the influence of soil fertility on the nutritional quality of crops and the animals fed on those crops. These conflicts can be resolved only through long term studies. Such a study has been initiated at the Michigan Agricultural Experimental Station in 1945 and is planned for a 10 year period. Preliminary reports from this group indicate that the amounts and kinds of amino acids in milk proteins remain rather constant irrespective of the soil fertility conditions under which the cow's feed is grown. The same workers conclude that based on present data accumulated over a five year period, there is no justification for assuming that the level of soil fertility can influence the quality of cow's milk. Thus, L. Turk, (4) Head of Soils Science Department, Michigan State College states: "The theory that the over-all nutritive value of foods for man is favorably influenced by a fertile soil has not been proved."

The problems of nutrition are so vast that the sphere of competence of each individual expert is usually rather limited. There is no one competent to speak with authority on all of its intricate aspects. I therefore suggest that when problems of interpretation of nutritional data or information arise, that the following group should be included among those consulted. Each of them is composed of experts representing the different fields of nutrition.

1. Bureau of Human Nutrition and Home Economics, Washington, D. C.

2. Agricultural Research Administration.

3. United States Department of Agriculture.

4. Food and Drug Administration.

5. University of California Agricultural Extension Division.

6. Food and Nutrition Board, National Research Council.

We have had food faddism with us for centuries. It is not a new problem. We cannot in all fairness really generalize and exactly delineate the precise characteristics of the faddist. Some of them are undoubtdly unscrupulous while the author has known others who are extremely sincere in their beliefs. It is unfortunate that they cannot separate beliefs from scientific evaluation. In many ways the faddist serves a useful function something like our two party system in a Democracy. We are all aware that the efficiency of a Democracy is largely determined by the existence of informed electorate. In like manner I am sure faddism will continue to flourish as long as scientists continue to write for each other's education. An effort should be made to establish a better liaison between the scientist and the public. We must not continuously preach to those who are already converted.

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4. Turk, L. N.: Soils and Their Relationship to Food Production. Journal of Agricultural and Food Chemistry. 1:136, 1953.

# ABSTRACTS ON NUTRITION

DESAI, R. A. AND MOHILE, G. B.: *Epidemic dropsy in Nadiad.* Jour. Indian Med. Assn., 24, 7, Jan. 1955, 248.

In Nadiad, a town of 62,700 population, a serious disease affected 555 persons, and in those affected most members of the family likwise suffered the same symptoms. The disease had to be differentiated from beriberi and from starvation edema, filariasis, and epidemic hemorrhagic fever, the last being seen among soldiers in Korea. The oil of the argemone seed (the active toxic principle of which is sanguinarine) or, in other words, oil of mustard, was finally found to be the cause of the disease. It had a wide-spread symptomatology, but the striking features were edema of the legs and erythema of the legs. Other symptoms were general malaise, anemia, fever, gastro-intestinal upset and tachycardia. The mustard oil was detected in some of the foodstuffs eaten by the affected families, especially til oil, and peanut oil, and large stocks of argemone seeds were found in the oil mills of the district. Apparently few cases were fatal.

SHAH, M. J. AND LEWIS, R. A.: *Epidemic dropsy —Nadiad epidemic: observations on serum proteins and cortisone treatment.* J. Indian Med. Assn., 24, 7, Jan. 1, 1955, 245.

In an epidemic of so-called "epidemic dropsy" occurring in Nadiad, India, in 1953, the cause was believed to be the ingestion of mustard oil as a contaminant of other foods. Edema and erythema of the legs formed the striking features of the cases, one of which is described in detail. In treatment there was no response to antibiotics or antiamebic therapy. There was elevation of the urea and non-protein nitrogen level of the blood. Serum protein studies showed a marked reduction in the albumin fraction and a significant elevation of the alpha-two globulin. The institution of cortisone treatment caused a prompt fall in temperature and a gradual subsidence of all signs and symptoms, and there was a rise in the serum albumin but no change in the alpha-two globulin.

HAWKINS, C. F.: *Value of serum iron levels in assessing effect of hematinics in the macrocytic anemias.* Brit. Med. J., Feb. 12, 1955, 383.

A fall in the serum iron level is the first indication of effective therapy, and is the first response, in treating macrocytic anemias. The bone-marrow reversion is not complete until 32 to 72 hours. The reticulocyte response does not appear for several days. The test is useful if the level of the initial red-cell count is such (3,000,000 cells per c.mm. or more) that the reticulocyte change is slight or inconclusive, and in out-patients who cannot come daily for reticulocyte counts. It is helpful in severely ill patients in whom the earliest indication of effective therapy is needed, as waiting may be dangerous. The explanation of the fall to a low level is perhaps that the rate of release of iron from stores, possibly by enzyme action, cannot keep pace with the increased demand. It is interesting that, irrespective of the initial height, the level after successful therapy is similar in all. This figure may represent a state of physiological balance between the stores and the bone marrow. The test is an index of an increased turnover of iron in the body, and the low serum iron a measure of erythropoietic activity.

FISHER, M. AND BIGGS, R.: *Iron deficiency in pregnancy.* Brit. Med. J., Feb. 12, 1955, 385.

The steady fall in hemoglobin repeatedly reported to be characteristic of pregnancy, does not occur if iron is administered except in the small group of "non-responders." It would seem advisable to prescribe iron for all pregnant women. Where this is done, it is often unnecessary to do repeated hemoglobin estimations. A woman with 90 percent hemoglobin at term does better than one with a reading below 80 percent. The giving of iron through pregnancy usually obviates the need of blood transfusion.

BREBNER, H. AND WILKINSON, J. F.: *The nucleic acid content of bone-marrow cells in pernicious anemia.* Brit. Med. J., Feb. 12, 1955, 379.

Chemical estimations of nucleic acids were carried out on suspensions of blood and bone marrow cells. The cellular content of R.N.A.P. (ribonucleic acid phosphorus) is higher in pernicious anemia marrows than in hyperactive normoblastic marrows. Accumulation of R.N.A. in the cell is therefore a specific feature of megaloblastic hemopoiesis. The cells of pernicious anemia marrows and those of hyperactive normoblastic marrows contain approximately the same amount of D. N. A. P. (desoxyribonucleic acid phosphorus), the figures in each case being about 150 percent of values for blood leucocytes. This finding suggests that many cells of the pernicious anemia marrow are of proliferative type and are engaged in building up D.N.A. in preparation for mitosis.

COBLEY, J. F. C. C.: *Carbohydrate tolerance in pregnancy.* Med. J. Australia, Feb. 5, 1955, 171.

One hundred and fifty-eight pregnant women have been subjected to glucose tolerance tests at intervals throughout pregnancy. Carbohydrate metabolism as measured by the glucose tolerance test in pregnant women undergoes little change during pregnancy. The fasting blood sugar level of pregnant women is within normal limits. The peak of the blood sugar curve in pregnancy occurs at the anticipated time in most cases, but can be expected to be delayed in some women. The fall of the curve to normal takes two hours in the majority, but is delayed beyond two hours in about 25 percent of pregnant women.

SLACK, G. L.: *Incidence of dental caries in children under 5 years old.* Brit. Med. J., Jan. 29, 1955, 260.

The incidence of dental caries in children under five is so great that the average child has 5 decayed teeth. There are not enough dentists in England to take care of this situation on a reparative basis. Slack notes the

success of fluorination of water in the U.S.A., and notes that this plan is to be carried out in England also. At present the most effective treatment is to teach the child to rinse out the mouth with water after every meal.

TUTTLE, W. W., DAUM, K., LARSEN, R., SALZANO, J. AND ROLOFF, L.: *Effect on school boys of omitting breakfast.* J. Am. Dietetic Assn., 30, 7, July 1954, 674.

Data were collected from 25 school boys 12 to 14 years of age over a period of 26 weeks to show the effect of omitting breakfast on their physiological responses, attitudes and scholastic attainments. The following findings were made,—neuromuscular tremor magnitude, choice reaction time, grip strength, and grip strength endurance were not affected by omitting breakfast. Maximum rate work and maximum work output were significantly less in the late morning hours during the period when breakfast was omitted. It was the opinion of the school authorities that the omission of breakfast exerted a significant detrimental effect both on the attitudes and scholastic attainments of the boys.

BOLTON, J. H.: *Food, the appearance of the tongue, and the appreciation of bone vibration.* Med. J. Australia, Jan. 1, 1955, 10.

Bolton has correlated dietary histories, tongue appearances and vibration sensitivity. So far as the tongue is concerned, he has elaborated on the appearances of the tongue as papillary atrophy proceeds and emphasizes the role of edema of the tongue which is a transitory but important phase of the changes. The ultimate result is a slick, red tongue. In estimating vibration sense he has employed two methods which do record smaller changes than are obtained using the usual, large tuning fork. The total results were analyzed statistically by the method of multiple regression, and indicated that the tongue changes, leading to atrophy, are due to the ingestion of something less than first-grade protein and have no connection with avitaminosis. Fine grades of bone vibration loss are indicative of deficiency of B-vitamin-containing foods.

SINHA, R.: *Diabetes and pregnancy.* Calcutta Med. J., 51, 10, Oct. 1954, 328.

This review of the title subject is very much in line with the attitudes of the majority of American obstetricians, pediatrists and internists. Sinha recommends interruption of pregnancy by induced labor or section, not at any standardized period, but at a time when the fetus has obtained a maximum maturity compatible with its own and the mother's welfare. Strict diabetic management all the way through pregnancy with chemical controls is important. He questions the value of hormonal therapy unless there is chemical evidence of placental failure. To the baby, parenteral glucose and antibiotics from birth are needed. He makes the point that a new concept of the "pre-diabetic" father has to be considered inasmuch as the fetuses of such fathers may also be too large.

# EDITORIALS

## ARTERIOSCLEROSIS

As all physicians know, hardening of the arteries represents bed rock in modern medicine, being a condition which causes directly many diseases of varying symptomatology, is essential to coronary disease and cerebral accidents, and which, finally, appears as the stumbling block to any effort to increase greatly not only the span of human existence but to make the present years of expectancy enjoyable.

Murray Israel, M.D., Instructor in medicine at New York Medical College, presents, in this issue of our journal, an article which it would be well for us all to study diligently. While his logic and his modesty force him to admit that he has not, as yet, come up with a complete answer to the tremendous problem of atherosclerosis, it is nevertheless obvious that he has made one of the most important studies thus far in that direction.

The "aging" process appears to be the process of atherosclerosis and the latter, in the light of his present research, seems to be the natural result of a metabolism in *decrescendo*. By stimulating metabolism with thyroxin in organic union with vitamin $B_{12}$, plus the use of lipotropic agents, vitamins and a high-protein, low-cholesterol diet, he has without doubt obtained a rejuvenation of a new kind.

His work deserves attention first because of its practical application to coronary disease, which it has been shown to benefit very greatly. Furthermore, his work is likely to cause speculation with respect to many other problems, because his bold use of powerful therapeutic agents is not only harmless, but provides at least a down-payment on that priceless desideratum—an old age of vigor and enjoyment.

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## CHRONIC GASTRITIS

Meadows and Lefeber (1) after analyzing the results of over 1,000 consecutive gastroscopic examinations in 14 years, state that the diagnosis of chronic gastritis has fallen into disrepute in their practice. Others have commented on the lack of a symptom pattern in chronic gastritis and the same gastroscopic findings may be present in persons with no complaint. They believe it possible that chronic gastritis (excluding gastric atrophy) represents only physiological changes and not intrinsic disease.

Before gastroscopy had become a common procedure, the profession had practically dismissed chronic gastritis as a diagnosis. Years before that, it was believed to be a real disease entity. Soon after gastroscopy came into wide use, the entity was again restored, simply because it was a common gastroscopic diagnosis.

It will obviously require several years more before the pendulum becomes stabilized. Chronic gastritis was always a convenient clinical diagnosis, particularly in patients with epigastric burning and distress but with-

out x-ray evidence of peptic ulcer. No doubt, in many of these cases, a duodenal ulcer had been overlooked, and duodenal ulcers are not difficult to overlook. At all events, the treatment was virtually the same as for peptic ulcer and relief usually was obtained. We will have to leave the final decision to the gastroscopists as to whether or not chronic gastritis actually exists.

(1) Meadows, J. C. and Lefeber, E. J.: Gastroscopy: a 14 year survey of over 1,000 consecutive examinations. Ann. Int. Med., 42, 1, Jan. 1955, 69.

# BOOK REVIEWS

ROENTGEN DIAGNOSIS OF ACUTE INTESTINAL OBSTRUCTION. Claude Olivier, Masson and Co., 120 Blvd., Saint Germain, Paris 6. 3,300 francs.

Fifteen years' experiences in acute intestinal obstruction are summarized and analyzed from cases seen in the Salpetriere. Mechanical, inflammatory and reflex lesions are described. Barium both by mouth and by enemas are used in diagnosis. Fifty illustrations are given and described in conjunction with the clinical findings. Unusual instances of visceral torsions, acute pancreatitis, renal colic and retroperitoneal hematomas receive attention, as well as other unusual associations with obstruction. The book has a hard cloth binding. It will prove of thought-provoking interest to all surgeons and clinicians.

FIBROSIS OF THE LIVER IN WEST AFRICAN CHILDREN. J. H. Walters and J. C. Waterlow (Medical Research Council Special Report Series No. 285). Her Majesty's Stationery Office, Atlantic House, Holburn Viaduct, London, E. C. 1, England, 8 s. 6 d.

The present report runs to 100 pages, about 25 of which are taken up with reproductions of photomicrographs from liver biopsy specimens.

Spread out along the River Gambia in British West Africa is a community of simple peoples whose existence lies at the mercy of nature and who are constantly exposed to the twin problems of undernutrition and disease. At the end of the long dry months between harvests until the new crops of rice and maize are reaped, food is for a time scarce and poor in quality. During this hungry season malarial transmission is at its peak.

Babies and young children are the first to suffer from the privations caused by lack of food. Almost all infants in the first two years of life have enlarged livers, sometimes without obvious symptoms, and overt liver disease is frequently seen even in quite young children. The authors of this Report, who worked in the Gambia as members of the Council's Human Nutrition Research Unit under the direction of Professor B. S. Platt, have studied, by means of biopsy specimens, the natural history of liver fibrosis occurring in the children there. They have cast their net wide, and, starting from the advanced diffuse stage which may be associated with serious clinical disturbances, have gone on to trace the disease back through the stages occurring in childhood, when there is often symptomless enlargement of the liver, to its origins in the earliest years of life.

At first sight, and in view of recent experimental work, the whole condition might well be attributed to undernutrition alone. But examination of the environmental background shows that both malnutrition and malaria occur most frequently and with greatest effect at that age in the child's life when liver lesions are first found. The authors conclude that neither factor alone is a sufficient cause, and they advance the hypothesis that malaria evokes a localized inflammatory reaction in the portal tracts which is encouraged by nutritional deficiency. If the state of undernutrition continues, the fibrosis may progress and become diffuse, and the risks to life increase proportionately; but by improving the nutritional state the initiating lesion can be halted and the infant will recover with nothing more serious than tiny residual scars in the liver.

The theory of a dual origin of liver fibrosis here put forward makes an important contribution to the study of this disease. It may also have a wider significance when applied to the natural history of other diseases occurring in undernourished communities, and in this way represent a new development in our approach to the study of pathological conditions on a geographical basis.

FOURTH ANNUAL REPORT ON STRESS. Hans Selye and Gunnar Heusser. Acta, Inc., Montreal, 1955.

In 1950 the monograph *"STRESS"* was written with the object of reviewing the entire literature on this topic (including the adaptive hormones and the diseases of adaptation). Since 1951 the ANNUAL REPORTS ON STRESS have been published as yearly supplements, which act as an index facilitating the task of keeping abreast of the rapidly growing literature in this field. The structure of these Annual Reports corresponds to that of "STRESS," but each volume is an independent entity in itself.

The ANNUAL REPORTS ON STRESS consist of a *detailed critical review by the editors* of the most important problems and results of each year's clinical and laboratory research and a discussion of the Stress-Concept, as it presents itself at the time of publication. Special points currently of interest are also discussed in the form of *independent original articles by* invited *guest-authors* who are internationally recognized leading authorities in their fields.

The second part of the book is a classified index to current literature on Stress, the General Adaptation Syndrome, the adaptive hormones (ACTH, STH, corticoids, adrenergic hormones, etc.) and allied subjects. The data in this index are *classified according to a system specially devised so as to permit—even to the uninitiated—the rapid compilation of the whole world literature, or any topic within the domain of Stress-Research.*

Hans Seyle unquestionably made one of the most remarkable discoveries in medical history when he noted that specific bodily reactions occurred in response to

non-specific forms of stress. Not only is Seyle to be congratulated upon such a fundamental observation, but he is also to be congratulated upon tenacity and industry which he continues to show in following up the infinite consequences resulting from his major theory.

OPERATIVE CHOLANGIOGRAPHY. Technique, diagnosis, praxis. Priv. Doz. Dr. Walter Hess. Preface by Prof. Dr. R. Nissen. 201 pages, 150 illustrations. Georg Thieme, publishers. Stuttgart 1955. $10.00.

"Operative Cholangiography" is based on the findings of the Department of Surgery in Basel. Hess describes the procedure of cholangiography as it is commonly used and its refinement in connection with manometry. This method was described by Carnot, Caroli, P. Mallet-Guy and Guy Albot. They have all published extensively on this subject. The first part of the book contains a thorough description of this method, which has been worked up and developed in France. In the U. S. A., Roy Upham reported on these methods in 1954. The author presents further, the method of L. Leger for filling of the duct of Wirsung (pancreatography).

Hess' tremendous material is corroborated by surgical findings, which are of the utmost value. The second and third parts of the book deal with the diagnosis and surgery of the bile ducts under cholangiographic control. Hess gives a thorough description of bilio-pancreatic reflux and the roentgenological changes of the pancreatic ducts. Special chapters deal with chronic pancreatitis in gallbladder surgery and with tumors of the bile ducts and the pancreas. The combined methods of manometry and cholangiography are apparently able to unravel many problems in this field.

The book is well written in German. It it so important that we hope it will be translated into English. The illustrations are clear. Each one is accompanied by a drawing, so that fine details can be noticed by the reader. Besides, the history of diseases is added, so that the illustrations are extremely instructive. Rudolph Nissen, the director of the Surgical University Clinic in Basel, has written a very interesting introduction. Thieme has done a very good job in the publishing of this book. We recommend it most highly to the gastroenterologist, the surgeon, the roentgenologist and to all those interested in this very important field.

Franz J. Lust

# GENERAL ABSTRACTS OF CURRENT LITERATURE

COUJARD, R., CHEVREAU, J., DAUM, H. ET MAILLET, M.: *Lesions of the Digestive Tube.* Arch. Mal. App. Dig. T. 43, No. 9-10, Sept-Oct. 1954.

The authors explain how the study by one of them, of the mode of action of the morphogen hormones by the medium of the autonomous nervous system, brought them to extend the notion of Reilly's phenomena, after the unilateral destruction of the ganglia or of the sympathetic fibers (especially of the genital zone).

Following various maneuvers, (washes with carbolic acid of the ureter, transversal fistula of the ductus deferens, introduction of various foreign bodies in the nuclei of the base of the brain), they observe early general results, of which one important part concerns the digestive tube.

They obtain thus gastric ulcers, infarcts of the gastric wall, infarcts and ulcers of the colon and also a cirrhosis of the biliary ducts.

These lesions are accompanied frequently, with infarcts of the cardiac muscle, and of the adrenal glands, and very often with lesions of the kidneys.

Later lesions, equally constant, appear after the surgical constitution of the transverse fistula of the ductus deferens, or after the lesions of the sympathetic fibers of the duct of the submaxillary gland, or after the wash with carbolic acid of the spermatic artery.

The gastric ulcers are often scarred and present a transformation into stratified squamous epithelium with a horny layer.

The young ulcers habitually coexist. The ulcers of the small intestine and of the colon, are not rare and a tumor can even develop on the scar of the ulcer.

Troubles in spermatogenesis are often very definite.

It appears that a narrow sympathetic band exists between the salivary gland and testicle.

The lesions of the autonomous nervous system of the salivary glands impede spermatogenesis (possible mechanism of the orchitis after mumps) and in exchange the lesions of the genital sphere can sometimes, with surprising frequency, determine adenomatous tumors of the salivary gland.

The washes with carbolic acid or the sections, described above, certainly reach the sympathetic fibers, as well as a localized lesion of the nuclei of the base of the brain.

The authors wish to establish that a localized lesion of the autonomous nervous system, peripheral or central, shows itself at a great distance, noting that unilateral lesions are more serious than the symmetric ones.

The interest of this study is the trophic role of the autonomous nervous system, in the harmonious growth in which it could act as a coordinator.

Guy Albot

STEINBACH, H. L., ROSENBERG, R. H., GROSSMAN, M. AND NELSON, T. L.: *The potential hazard of enemas in patients with Hirschsprung's disease.* Radiology, 64, 1, Jan. 1955, 45.

Four cases have been collected in which death resulted from the use of barium enemas in Hirschsprung's disease and one in which severe shock resulted. Water intoxication may occur due to rapid absorption of water from the colon. It is also possible that reflex cardiac inhibition and shock may be produced by abnormal dis-

tention of the colon. It is recommended that isotonic saline instead of water be used in making up the barium mixture. Also, the smallest amount of solution necessary should be injected under low pressure, and as much as possible of the fluid be recovered after the procedure has been completed.

RICE, J. O. AND WILHELM, M. C.: *Duodenal diverticulum: report of a case of acute perforation.* Bull. Mason Clin., 8, 4, Dec. 1954, 139.

A case is presented of an acute perforation of a diverticulum of the duodenum in an 81 year old male. Perforation is an uncommon complication of duodenal diverticulum. He presented an acute abdomen with tenderness and rigidity in the upper right quadrant. A diagnosis of acute cholecystitis was made. At operation the gallbladder was chronically inflamed and contained stones. However, an area of necrosis led to the finding of a perforated duodenal diverticulum in the second portion of the duodenum, which was removed, as well as the gallbladder. He made an uneventful recovery. Post-operative x-ray studies, however, revealed a second diverticulum of the fourth portion of the duodenum, which was not noted at operation.

ANDERSON, R. F. AND MILLER, M. J.: *Submucous lipoma of the ileum with intussusception: a case report.* Bull. Mason Clin., 8, 4, Dec. 1954, 135.

Only 10 percent of benign tumors of the small intestine are lipomas, and only 1 in 10 of these is found by the surgeon operating for symptoms due to that lesion. The other 90 per cent are all incidental surgical or autopsy findings. The symptoms of submucous lipoma are essentially those of small bowel obstruction, intermittent or progressive, secondary to intussusception. Repeated episodes suggesting acute bowel obstruction that clear up spontaneously are not uncommon, and in a person whose abdomen has not previously been operated on, are highly suggestive of intermittent intussusception. Bleeding is not typical of this particular small bowel tumor. A case of a large submucous lipoma of the small intestine is presented as a clinical rarity, and to illustrate the typical picture of intermittent, then progressive intussusception in an adult.

DICK, A. P.: *Association of jejunal diverticulosis and steatorrhea.* Brit. Med. J., Jan. 15, 1955, 145.

Dick describes a case of jejunal diverticulosis complicated by steatorrhea, macrocytic anemia and glossitis. Parenteral crude liver extract produced a complete remission of the glossitis and macrocytosis. Parenteral refined liver extract, oral folic acid, and massive vitamin B therapy had no effect on the glossitis, while the macrocytosis showed a variable response to refined liver extract and folic acid. Improvement in the diarrhea and general health occurred after a course of chlortetracycline, and the glossitis and anemia remained in remission, without further use of crude liver extract, for a period of 8 months. It is suggested that the multiple jejunal diverticulosis was responsible for the steatorrhea, and that stagnation and infection in the diverticula may have been the most important factor in producing the small intestinal dysfunction.

MIRVISH, L.: *The management of hematemesis and melena.* S. African Med. J., 28, 50, Dec. 11, 1954, 1055.

A study of 108 cases of severe gastrointestinal hemorrhage and 21 cases of mild bleeding, all hospitalized, is presented. Bleeding ulcer and bleeding from esophageal varices were the main lesions encountered. In South Africa, alcoholic cirrhosis is more common among the European than the native groups. Alcohol sometimes seemed to provoke hemorrhage from a gastric ulcer (4 cases). The authors' management of severe gastrointestinal bleeding closely resembles that used in most American clinics today. He insists on making a diagnosis of the site of bleeding as soon as possible. His results were closely parallel to those obtained in our best American hospitals.

JOSKE, R. A.: *Pancreatitis following pregnancy.* Brit. Med. J., Jan. 15, 1955, 124.

A fairly complete report of 6 cases of post-partum pancreatitis shows that the majority of the cases had gall-stones. Cholecystectomy was done in most of the cases. Two were treated conservatively with antibiotics. All made good recoveries. Joske suggests that the term "post-partum pancreatitis" be used to indicate a definite clinical subgroup in which pregnancy has something to do with the pancreatitis, even though the nature of the relationship is, at present, quite unknown.

WALLIS, H. R. E.: *Tuberculous mesenteric adenitis in children.* Brit. Med. J., Jan. 15, 1955, 128.

Wallis draws attention to the importance of tuberculous abdominal adenitis as a cause of fever and abdominal pain in children. Twenty cases are reviewed, including cases presenting with pain, fever, attacks resembling acute appendicitis, tuberculous rheumatism, and the celiac syndrome. In treatment, Califerol (50,000 units daily for 6 weeks) is recommended as a means of expediting the natural process of healing. The disease, which is as common as pulmonary tuberculosis is considered to be due to drinking infected milk.

FRECH, K.: *Rectography.* Fortschr. Gebiet d. Roentgenst. 78, 1, 53. Jan. 1953.

Rectography by means of contrast "spumanstyli" forms under ordinary conditions a connected coat on the inside wall of rectum, ampulla and end of sigmoid flexure and therefore the roentgenologic observations and descriptions of the picture will be the same as has been usual for a long time in the roentgenologic examination of other segments of the alimentary tract: judgment of the position of the organ, its caliber, the outline of the shadow, and the course and forms of the folds of the mucous membrane. Defects, disorders or missing of the relief are of the same diagnostic value as a plain course and a proved stop.

It must be the aim of further studies to prove still more the usefulness of rectography for the general examination of the colon and especially in adults and children. Especially if there is suspicion of a carcinoma of the rectum it is absolutely essential to stick to a proper examination. The rectography will not replace the other efficient methods of examination.

Franz J. Lust

ALBOT, G. AND LEGER, L.: *Ligature of the common hepatic artery in chronic cirrhogenous hepatitis. Mechanism of the action according to results obtained in cases of initially anascitic cirrhoses.* (Presse Médicale T. 62, No. 86, December 25th, 1954, p. 1794.)

It is customary to restrict ligature of the common hepatic artery to cases of decompensated cirrhosis accompanied by ascites or by hemorrhagic varicosity of the oesophagus. However, the reaction of this operation on the biology and histology of these advanced cirrhoses is very difficult to estimate as sclerous cicatrization and disruption of the structure of the liver are already of such importance that modifications due to partial interruption in the arterial flow run the danger of being passed over unnoticed.

Failure to operate in cases of initially ascitic cirrhoses, which has been a tenet up to the present time, would be unassailable if there was any medical treatment available to interrupt the course of events: in actual fact, such is not the case and sooner or later, these patients reach the stage of decompensation, ascites and death.

The authors report the first attempt at treatment by ligature of the hepatic artery in these incipient cirrhoses. They endeavor to explain exactly in three cases in point the action of the operation and its mechanism.

Contrary to the currently accepted view, these cases reveal that ligature of the hepatic artery does not cause a fall in portal pressure and that pre-operatory variations in this pressure are due to fluctuations in general arterial pressure: and if such is the case, this operation with its undoubted action upon the development of morbidity must be explained by some other mechanism.

The effect on the functional examinations of the liver has hitherto been studied in a very haphazard fashion and only with reference to ascitic cirrhoses or hemorrhagic cirrhoses: they were formerly unknown in cases of anascitic cirrhosis where the facts are however simpler. In the 3 cases studied, the ligature did not have any noticeable effect on the aggregate protein content of the blood nor that of the albumin and globulins as happens in ascitic forms (a fact which confirms Rienhoff's hypothesis according to which the improvement of proteins in ascitic cirrhosis is due to the drop in the escape of the blood proteins into the ascitic liquid.) The regular improvement of the bromosulphonphthalein and its early results supports the theory that it is the result of accelerated flow of the portal blood. Passage tests (diuresis, lactosis and hippuric acid) have not shown any considerable improvement during the succeeding months, any more than have the Mac Lagan and Kunkel tests. On the other hand, the Rec Colloidal Test carried out with the antigen and according to the technique described by Guy Albot and M. Corteville, gave a definite reaction in 3 cases in which it veered from a strong reaction to a normal one, quite permanently in 2 cases and temporarily in 1. Therefore the modifications in these functional examinations are undeniable but complicated: their late appearance would seem to suggest that they are not brought about through the intermediary of a decline in portal pressure, but rather through the fact that they promote regeneration of hepatic parenchyma.

In only one of the three cases did the authors have a sufficient time lapse to compare the histology of the liver before and 26 months after the ligature, with four interim studies: this case enables them to assert that this operation promotes the regeneration of the parenchyma and checks proliferation of the conjunctive tissue, as the appearance of the liver, sampled either by injection biopsy or by surgical biopsy, proves. This result was a late development and its exceedingly spectacular nature seems due to the fact that the operation was carried out early on a patient with incipient cirrhosis, biologically decompensated, but clinically still latent. This prolonged action is late in manifesting itself and fits in badly with the hypothesis of a decline in the level of portal pressure: it is more compatible with the hypothesis of Chenoweth, Berman and Hull who consider that the operation restores the speed of portal flow and thus promotes regeneration of the hepatic tissue whilst preventing the spread of inflammatory conjunctive lesions.

HILLEMAND, P. AND BARRE, Y.: *Etiology and medical therapeutic of diaphragmatic hernias.* Presse Médicale 1954, No. 84, 1791-1793.

The ascent of the cardia through the oesophageal hiatus presupposes a certain number of isolated or collective disorders as follows:

a) Often a muscular or peritoneal predisposition.

b) A disorder in the tonicity of the pillars (controlled by the sympathetic since the phrenic is a motor nerve) due to a vegetative imbalance, an inflammatory rheumatic area, or a digestion factor. Which is to say that endocrine disturbances may play a neurovegetative or a muscular nutritional role.

In general our etiological results were as follows:

*Mechanical abdominal compression* may be extrinsic. It corresponds to diaphragmatic hernia cases in carriers of "lombostats" for example.

Intrinsic compression is rare. The role of pregnancy is probably more endocrine than mechanical. Ascites, even distended, is rarely at fault.

*Rachidian lesions*: The following may be observed:

1.—A post traumatic Kummel-Verneuil type aspect.

2.—An aspect of scoliosis with more or less pronounced angularity.

3.—A definitely inflammatory appearance consisting of "becs," syndesmophytes, or more posterior attacks and lesions of costo-vertebral joints between D7 and D10 and which may accompany the preceding. The role of such rachidian lesions seems important to us due to their frequency (¾ of all cases) even in very young subjects, due to their often segmentary seat at the level indicated and to a certain improvement already obtained in our therapeutic efforts in this direction.

*Endocrine Disturbances*: Can be classified under three syndromes:

1.—*Genital disorders*: a) In the female, D. H. occurs 5 times out of 8. The menopause, the period at which such disorders most frequently commence, is ordinarily

difficult and prolonged.—During the period of genital activity, D. H. may be observed to appear from the age of puberty on, then in women suffering from an early or prolonged "hyperfolliculin" condition and lastly during pregnancy.—One might be tempted to group these two periods of before and after the menopause under their common pituitary factor of gonadotrophin excess with folliculin response exaggerated or absent depending on the ovarian age.

b) In men the genital factor is less important, manifesting itself by functional deficiency either through a lowering of hormone secretion observed in the urine, or, more frequently, through the interference of a spasmophilic or hypothyroid component.

2.—*Spasmophilic conditions,* as is well known, are quite frequent. They play a definite but rarely isolated role in the mechanism of D. H. and treatment of such conditions has often improved digestive disorders.

3.—*Hypothyroidism* has externalized itself in 80% of our cases with a lowering of basal metabolism from —10 to —37% and an increase of cholesterol parallel with an ordinarily moderate clinical syndrome and exceptionally an aspect of myxoedema, which points up the value of instrumental measurement of metabolism under circumstances which render it truly "basal," since the radioactive Iodine test is sometimes definitely lowered and sometimes slightly raised as in certain cases of pubescent goiters.

4.—*Association* of these groups may give the following:— in some cases, the triad made up of gonadotrophin excess, spasmophilia and hypothyroidism;—in others, a combination of hypothyroidism and spasmophilia in which the latter element sometimes conceals the clinical aspect to the point of roughly simulating hyperthyroidism.

In conclusion, *the therapeutic side* of the question is interesting. In the case or rachidian disease, we tried dorsal radiotherapy to relieve congestion resulting in functional improvement only of the D. H. but no radiological improvement. We then tried concentric transverse ionisation with results which appear encouraging.

The results of endocrine treatment are more definite. As regards the genitals, before the menopause, progesterone played an adjuvant role. After the menopause, we might stress the fact that only one of all our cases of D. H. responded to estrogens.—Pure spasmophilic treatment effected cure in two months of a D. H. in a 20-year-old girl.—Lastly, by means of the *thyroid treatment,* we are obtaining a high rate of functional improvement and marked or total radiological improvement in roughly half of the cases.

We should like to insist, in closing, on the necessity of prolonged treatment or risking a relapse, and to offer the hope that an endocrine-physical therapy combination may set a patten for medical treatment of D. H.

DAYANADA, RAO B.: *Volvulus of the small intestine.* Jour. Indian Med. Assn., 24, 5, Dec. 1954, 173.

Fifteen cases of volvulus of the small intestine are described. After the onset of severe pain and vomiting the patient's condition may remain remarkably good for 4 or 5 days. Early operation is necessary. At operation the procedure of choice is primary complete evisceration, followed by a process of replacing the small gut back in place starting at the jejunum. This permits inspection of the mesentery, and automatically unravels the twist responsible for the condition.

SUMMERS, J. E.: *Cardiospasm.* Am. Pract. and Dig. Treat., 6, 1, Jan. 1955, 44.

Cardiospasm is a non-organic stenosis of the lowest portion of the esophagus associated with loss of ganglion cells in the cardiac esophageal muscle. Cancer must be ruled out in every case of dysphagia. Rupture of the circular muscles of the cardia, necessary for the relief of cardiospasm, can be accomplished by the use of the hydrostatic dilator or by the Heller type of operation which consists of the incision of all layers of the lower esophagus down to the mucosa. This operation is safe, gives good results and should be used more frequently.

ELKAN, W.: *Acute mesenteric vascular occlusion following mumps.* J. Int. Coll. Surgeons 20, 3, 259. Sept. 1953.

Acute mesenteric vascular occlusion is one of the most serious abdominal catastrophes, with a mortality rate above 90%. The mortality remains high because the condition is rarely diagnosed preoperatively. This is due to the low incidence of the condition (0.02%) and the absence of a typical pathognomonic picture. The salient clinical features of mesenteric vascular thrombosis are described. It is suggested that this entity be kept in mind in all cases of mysterious intra-abdominal conditions and that operation should be undertaken as soon as the diagnosis is made or suspected, even if the patient's condition appears hopeless. Wide resection must be done beyond the lesion, regardless of the amount of intestine removed. Anticoagulant therapy should be started immediately to prevent spreading thrombosis. The etiologic factors are discussed and a new factor (parotitis) is described reporting a case of successful resection. (32-year-old male.)

Franz J. Lust.

BROWN, C. H. AND INTRIERE, A. D.: *Benign ulcers of the greater curvature of the stomach: report of 2 cases.* Cleveland Clin. Quart., 22, 1, Jan. 1955, 29.

There is a high ratio of malignancy in ulcerative lesions along the greater curvature of the stomach. In fact, benign ulcers in the pars media of the greater curvature are relatively rare. Of benign, histologically proved, gastric ulcers of the greater curvature, only 40 cases have been described, exclusive of autopsy material. When a benign ulcer occurs on the greater curvature, there are likely to be ulcer or ulcers elsewhere, especially on the lesser curvature. Spasm of the pylorus and antrum, associated with ulcer anywhere in the stomach may produce a deceptive x-ray appearance of malignant filling defect. In all cases of ulceration of the greater curvature radical surgery is advisable inasmuch as malignancy may not be discovered on frozen sections, only to be found on paraffin sections.

## "REMARKABLE" EFFECT OF ATABRINE CITED IN TREATING PETIT MAL

PHILADELPHIA—Clinical experience confirming previous findings that Atabrine, the antimalarial, has a "remarkable effect in the control of petit mal seizures" is reported in the *Journal of the Albert Einstein Medical Center.* (3:12, 1954).

The statement dealing with Atabrine's effectiveness is contained in a review of epilepsy by Dr. Matthew T. Moore, Department of Neurology of the Albert Einstein Medical Center. The review covers current drugs, therapeutic methods, surgical procedures and general considerations in the management of epileptic seizures.

Atabrine was given to a group of patients by Dr. Moore in order to evaluate the conclusions of an earlier team of investigators. He states claims of its "remarkable" effect were "completely borne out." Control of seizures continued even after Atabrine had been discontinued for several weeks.

The antimalarial was given alone in a dose of 0.1 gm. twice daily for one week, then 0.1 gm. daily for several weeks. Treatment was then terminated unless a seizure recurred, at which time medication was resumed. For mixed seizures Atabrine was used in conjunction with other anti-epileptic drugs.

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## PRESCRIPTION SPECIALTY: VI-THYRO

WHAT THE PRODUCT IS: Vi-Thyro is a complete and effective thyroid preparation containing the equivalent of one grain U. S. P. thyroid activity, together with adequate amounts of thiamine, riboflavin, niacinamide, pyridoxine, calcium panotothenate, vitamins B-12, A, D, ascorbic acid, alpha tocopherol, choline, inositol, methionine, iodine, magnesium, and manganese in each capsule.

WHAT IT'S FOR: Vi-Thyro is a specially designed formulation providing effective and dependable thyroid substance together with metabolic elements in one capsule. Vi-Thyro is indicated wherever increased activity is desirable.

HOW ADMINISTERED: Vi-Thyro capsules are taken orally.

ADVANTAGES: Vi-Thyro is the only thyroid preparation which contains all necessary factors in an odorless, tasteless, brown soft gelatin capsule. The thyroid substance contained in Vi-Thyro is derived from a special processing of the whole thyroid gland which removes fats, oils and moisture without loss of activity.

HOW SOLD: In amber-colored bottles of 100 capsules.

PRICE TO PHARMACIST: $3.79.

WHO MAKES IT: J. B. Roerig and Company, division of Chas. Pfizer & Co., Inc.

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## GUM CHEWING AS RELATED TO PLAQUE pH

Subjects who chewed gum after rinsing the mouth with a glucose solution showed less tendency toward acid formation than when no chewing took place, Drs. A. A. Yurkstas and William Emerson of Tufts College Dental School, Boston, reported at the 33rd general meeting of the International Association for Dental Research in Chicago.

The effect of gum chewing on dental plaques was evaluated through pH reading on 45 subjects. Tests were alternated so each subject would serve as his own control.

A pH drop below 5.5, which has been termed "the critical level of decalcification," occurred 50 times among abstainers from gum and 14 times when the same subjects chewed gum after the rinse, the investigators said. Minimum pH readings averaged below 5.5 in seven subjects under control conditions, but only one fell into this category after chewing gum.

Among subjects who chewed gum after every meal for two weeks, no change in the activity of plaque material due to increased ingestion of sugars could be demonstrated.

Experiments at Tufts laboratory of oral physiology indicate, said the investigators, that "stimulation of saliva by chewing results in an increased alkalinity," and that "the oral clearance curve for carbohydrates in chewing gum resembles the salivary flow curve."

"The evidence that sugars are causative agents in producing tooth decay is overwhelming, but to imply that all sugar-containing foods are dangerous is not in keeping with the results of scientific researches," they said.

Drs. Yurkstas and Emerson cited recent Swedish findings to the effect that 100 pounds of sugar a year in a soluble or rapidly-clearing form can be added to the diet without a significant increase in caries.

Not all chewing gums result in the magnitude of salivary secretion, they reported, nor do they inhibit pH drop in the same degree. Of three gums used after a glucose rinse, one (Dentyne) was followed by an average drop of 0.40 pH units and the others by 0.62 and 0.71 respectively. Lower sugar content, as well as greater saliva-stimulating capacity, may account for the result, the investigators believe.

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## ATABRINE FOUND EFFECTIVE AGAINST PETIT MAL ATTACKS

BOSTON — The antimalarial drug Atabrine effectively combats petit mal attacks in epilepsy, it is reported in the *New England Journal of Medicine* (261:897, 1954).

Drs. Douglas T. Davidson and Cesare Lombroso of the Harvard Medical School note that Atabrine was useful against petit mal seizures, either alone or in combination with convulsions. Most patients in the series had failed to respond to other methods of treatment. The antimalarial was administered in 0.1 gm. tablets, in dosages ranging from 0.1 to 0.4 gm. a day.

There is considerable agreement among clinicians today on the principles of treatment for epilepsy, the authors say. Most concede that the drug to be used, and the dose, must be individualized due to each patient's variation in tolerance and need for medication. Effects of full doses of the least toxic drug should be tested first and the drug withdrawn if therapy proves unsuccessful. When one drug used singly fails, seizure control is often achieved by a combination of drugs in full dosage, the Boston doctors say.

They caution against sudden withdrawal of effective medication as likely to trigger a series of seizures.

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## MILK FORTIFIER

First clinical reports of the use of a pediatric milk fortifier containing lysine, an essential amino acid, were made today by a team of medical

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| Riboflavin | 10 mg. | Folic acid | 1.5 mg. |
| Niacinamide | 100 mg. | Menadione (vitamin K analog) | 2 mg. |
| Pyridoxine hydrochloride | 2 mg. | | |

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PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y.

scientists. They stated that this food supplement materially improves the nutritional and physical condition of underweight and poorly eating children, thus helping to build better bodies.

The new development in the field of pediatrics was discussed by Dr. Anthony A. Albanese, Chief of Nutritional Research of St. Luke's hospital, New York, N. Y., and his colleagues, Drs. Reginald A. Higgons, Gertrude M. Hyde and Louise Orto, the chemist member of the team. The report, published in the American Journal of Clinical Nutrition, told of a study with this new supplement on infants ranging in age from one to twenty-seven months.

The lysine supplement has now been made available to the medical profession as Lactofort by White Laboratories, Inc., Kenilworth, N. J. Lactofort is a tasteless white powder that dissolves readily in milk and contains, besides lysine, all essential vitamins as well as iron and calcium.

Dr. Edward R. Neary, Medical Research Director of White Laboratories, said other clinical studies with Lactofort are now in progress. He pointed out that, although lysine has been known for many years as an essential nutrient, only within the last year has it been made synthetically in commercial quantity by scientists of E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.

The St. Luke's scientific team said that comparable and parallel control studies were done on nine infants who received no lysine supplement during the period of observation which varied from three to twenty weeks.

"As a prelude to undertaking the detailed metabolic studies outlined above," they said, "chromatographic measurements of free blood lysine and total plasma protein levels of 15 infants (age 1 to 13 months) were performed bi-weekly for 2 to 3 months. These determinations disclosed that, as in adults, the blood lysine level is generally a better index of the nutritional state of infants than is the plasma protein level. In addition, it was found from these serial tests that the lysine level served as a good indicator of daily protein intake. This was especially true in infants with poor appetites arising fom a variety of causes.

"Subsequently, additions of lysine to the diet of some of the infants in this group (who were malnourished in terms of body weight and the lysine or total amino acid index) were found to improve appreciably the rate of weight gain with no increase in total protein intake.

"In the light of these considerations, the results of the preliminary studies encouraged us to undertake a systematic evaluation of the nutritional effects of lysine supplements. Our study showed that of the 15 infants studied the body weight and nitrogen balance of 5 were markedly improved by the addition of lysine to the diet. The infants in this group ranged in age from 6 to 26 months and generally maintained poor appetites. In every instance, prior to determining the effect of lysine supplements, improved nutrition was attempted by increasing the protein contein of the diet (4 to 6 Gm./Kg.). In most infants the increased protein intake caused a transient increase in weight gain and nitrogen-balance, which was soon followed by greater decreases in appetite and body weight."

As an example, the scientists reported, one of the fifteen infants under study was an infant about five pounds underweight for her age.

"Attempts to improve her nutrition by high protein or high caloric diets had met with consistent failure. However, when the lysine content of the diet was increased by supplementation, appetite was improved, high protein diets were better tolerated, and body weight increased. Concomitantly, the blood protein levels rose during the lysine-supplement period and fell in the post-control period. As might be expected from our previous experience, the free lysine levels of the blood were two to three times greater during the lysine period than in the pre- or post-control periods."

In summary the doctors said: "The results of our studies showed that the body weight and nitrogen balances of 5 of the 15 infants were markedly improved by the lysine supplement. Six of the children showed no spectacular weight gains, but urinalyses showed that more nitrogen was retained than before the lysine was added, indicating that these children gained in strength and sturdiness. Blood protein levels also increased during this period. The remaining 4 infants showed no observable improvement when lysine was added to their diet, indicating that lysine-fortified diets are only effective with children who are not getting adequate nourishment from their food. The growth rate of these 4 infants was already well above average. The results of these studies bear the implication that the nutritional value of many infant foods, including cow's milk, can be substantially improved by small additions of lysine."

Dr. Albanese, in stressing the practical implications of his study, has pointed out that lysine fortification of milk is a means of increasing its effectiveness in building muscle tissue in the infant and young child. He further emphasized that deficiency of lysine in the diet not only impedes the synthesis of muscle tissue, but apparently is also responsible for a depression of appetite. This appetite loss is then responsible for a further decrease in the youngster's intake of vital foods. Lysine fortification of milk seems to serve the dual purpose of stopping this vicious cycle by improving the child's interest in food and, simultaneously, improving his utilization of ingested protein. Lysine fortification is now made possible by the addition of small quantities of Lactofort, a lysine, vitamin-mineral supplement, to the daily diet of infants and children.

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## GEIGY INTRODUCES MEDOMIN, NEW KIND OF BARBITURATE

NEW YORK, N. Y.—A new kind of barbiturate called Medomin is being introduced to the medical profession in the United States by Geigy Pharmaceuticals here.

Differing structurally from other barbiturates, the compound has a 7-member ring attached to the barbiturate radical. Chemically Medomin is cycloheptenylethyl barbituric acid.

Described as a gently effective sedative and hypnotic with minimal side and after effect, Medomin is recommended for functional insomnia and anxiety-tension states. It is said generally to afford sound, refreshing sleep, and alert awakening without "hangover."

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Clinical investigators have also noted that when Medomin is used, patients remain responsive and can be roused from sleep when necessary.

Taken in divided doses as a daytime sedative-tranquilizing agent, the preparation has demonstrated relief of nervous tension as well as hypotensive effects in persons with elevated blood pressure.

Other studies show that Medomin is rapidly metabolized in the body and that it has a more favorable therapeutic index than phenobarbital, indicating a relatively higher degree of safety.

The product is available in bottles of 100, 250 and 1000 pink 50 mg. single scored tablets, similar sized bottles of yellow 100 mg. tablets, and bottles of 50, 250 and 1000 white 200 mg. tablets.

## INJUNCTION ENTERED IN CHLOR-TRIMETON INFRINGEMENT SUIT

Bloomfield, N. J., March 10—Schering Corporation, pharmaceutical manufacturers of Bloomfield, New Jersey, today announced that its infringement suit against Italian Drugs Importing Co., Inc., and others, involving Schering's "CHLOR-TRIMETON" patent, had been successfully concluded by the entry of a Final Judgment & Injunction.

Schering's Complaint had charged the defendants with infringement of the patent on its well-known antihistamine "CHLOR-TRIMETON," as well as trademark infringement, copyright infringement, and unfair competition. The injunction, entered on consent, enjoins the defendants from making or selling any of the compounds covered by Schering's patent, including the compound chlorprophenpyridamine maleate, which Schering markets under the "CHLOR-TRIMETON" trademark.

Francis C. Brown, President of Schering Corporation, stated that this infringement suit had been instituted in keeping with the Company's determined policy to protect its valuable position in the antihistamine field and to vigorously prosecute infringements of its patents.

## "ADVANCE" IN TREATMENT OF UPPER GASTROINTESTINAL DISORDERS REPORTED

NEW YORK, N.Y.—By virtue of its quick action and absence of side effects, Dactil represents an "advance" in the treatment of disorders of the upper gastrointestinal tract, according to a team of physicians representing several hospitals here.

They find it significant for "ambulatory working patients in whom immediate activity without side-effects is essential to prevent invalidism and loss of productivity."

The physicians are Julius Pomeranze, M.D., William H. Beinfield, M. D., A Allen Goldbloom, M.D., Ralph J. Lucariello, M.D., and Max Chessin, B.S., from the Department of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals; Metropolitan Hospital;

and the Bird S. Coler Memorial Home and Hospital.

In the *New York State Medical Journal* (55:233,1955), they report on a study of 63 patients. Disorders included pylorospasm and conditions associated with gastric motor dysfunction and biliary dyskinesia. Results were confirmed by x-ray examinations and clinical observations.

The authors conclude that Dactil "achieves therapeutic efficacy quickly and without undesirable effects."

"The activity of the drug became apparent within ten minutes of oral ingestion and in most cases was prolonged for three to four hours. It was this rapidity of action that focused attention upon its therapeutic value," the physicians point out.

Their study also "indicates an excellent parasympathicolytic activity confined to the upper gastrointestinal areas."

Dactil was developed by Lakeside Laboratories, Inc., Milwaukee, and introduced to the profession last year as the first in a series of new piperidols. Specificity, freedom from unwanted effects and rapid action have been found characteristic of these piperidols. Chemically Dactil is N-ethyl-3-piperidyl-diphenyl-acetate HCl.

As an example of the drug's efficacy, the authors report on four patients with pylorospasm and delayed emptying of the stomach unassociated with evidence of organic disease. The patients were fluoroscoped within ten minutes of the oral administration of 50 mg of Dactil. The stomach was seen to empty rapidly, indicating relief of spasm.

In 18 cases of gastric neurosis, 8 patients had "excellent" response and 8 "good."

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## BROAD-SPECTRUM ANTI-BIOTICS BOOST EFFECTIVENESS OF HYDROCORTISONE IN CURBING SKIN AILMENTS

BALTIMORE, April 27 — A synergistic effect between the broad-spectrum antibiotics and hydrocortisone when used locally in the treatment of many complicated skin diseases is reported by three investigators at the University of Maryland School of Medicine here.

The clinicians, Drs. H. M. Robinson, Jr., R. C. V. Robinson and J. F. Strahan, present their study of 1,655 cases treated with hydrocortisone free alcohol, hydro-cortisone acetate and hydrocortisone-antibiotic combinations in *Medical Times* 83:227-237, 1955.

"The addition of antibiotics to ointments or creams containing hydrocortisone free alcohol or hydrocortisone acetate did not alter the effect of the steroid, and had the additional therapeutic advantages of combating secondary pyogenic infection," the physicians said.

A concentration of 0.5 per cent hydrocortisone, or hydrocortisone acetate in lotion or oily base was found to be of value in the treatment of 60 per cent of the patients. Applications of the steroid effectively controlled or relieved symptoms of such conditions as atopic dermatitis, neurodermatitis, allergic contact dermatitis, pruritus ani and pruritus vulvae.

The investigators discovered no appreciable difference between the action of hydrocortisone free alcohol and hydrocortisone acetate.

Addition of tetracycline, Terramycin, neomycin, bacitracin or erythromycin to the steroid had the additional advantage of eradicating secondary pyogenic infection while the hydrocortisone acts on the underlying skin inflammation, according to the University of Maryland scientists.

A combination of Terramycin three per cent and hydrocortisone one percent in a specially formulated base is available as Terra-Cortril Topical Ointment—Pfizer.

Another study by these three physicians of 559 patients treated with topical steroid-antibiotic ointment appears in *Antibiotics Annual* (1954-1955). Results of this investigation also revealed the additive effect which occurs when a broad-spectrum antibiotic is combined with hydrocortisone.

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## BONAMINE USED TO CURE MORNING SICKNESS

A well-known motion sickness remedy is reported to be the most effective drug yet used by a New York physician in the treatment of nausea and vomiting in pregnancy.

Writing in the current issue of the *American Practitioner and Digest of Treatment* (Vol. 6, No. 3), Dr. C. J. McKenna reports, "Bonamine is definitely a safe compound to administer to the pregnant woman, and is the most effective drug ever used by the author for the control of nausea and vomiting of pregnancy."

Dr. McKenna treated 44 cases of nausea and vomiting of pregnancy with daily doses of Bonamine and found that a higher percentage of relief was obtained than with any previous therapy. He points out that, although the frequency of the problem in pregnancy is not generally appreciated, nearly 80 per cent of all pregnant women suffer from nausea and vomiting. He adds that the condition may be simply "morning sickness" or may progress to become a severe and dangerous pernicious vomiting of pregnancy. Complications at this stage can be fatal, he says.

According to Dr. McKenna, Bonamine was administered to patients suffering from uncomplicated vomiting and nausea of pregnancy. Some received short term therapy and others received the drug continuously into the fourth month. Twenty-two patients received 25 mgs. of Bonamine three times daily, 21 took it twice a day, and one patient once a day.

"Complete control of both nausea and vomiting, or elimination of vomiting with a few episodes of nausea were obtained in 40 of the 44 patients treated," he said.

Dr. McKenna declared that one patient in the group had excellent control of her nausea and vomiting, and also was markedly relieved of her severe recurrent migrainous headaches.

"Bonamine was found to produce relatively few side effects," Dr. McKenna said. "This unique new drug has a marked advantage inherent in its prolonged action, up to 24 hours. Thus a single bedtime dose of 25 to 50 mgs. will in the majority of cases carry patients through the notoriously difficult early morning hours and usually through the entire day."

Bonamine has been widely used in the past for all forms of motion sickness and vestibular disturbances. The drug is marketed by Pfizer Laboratories, division of Chas. Pfizer & Co., Inc.

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The RESIONS offer two effective compounds for treatment of almost any diarrheal condition found in clinical practice.

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RESION P-M-S is intended specifically for rapid control of those rare diarrheas caused by Gram-negative organisms; to prevent secondary bacterial infection; in mycotic diarrhea following the use of the broad-spectrum antibiotics, and to inhibit the enteric growth of *C. albicans* (Monilia).

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| Polymyxin-B sulfate | 125,000 units |
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Supplied: RESION, in bottles of 4 and 12 fluid ounces. RESION P-M-S, bottles of 4 fl.oz.

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PRO-BANTHINE® FOR ANTICHOLINERGIC ACTION

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*Pro-Banthine consistently controls gastrointestinal hypermotility and spasm and the attendant symptoms.*

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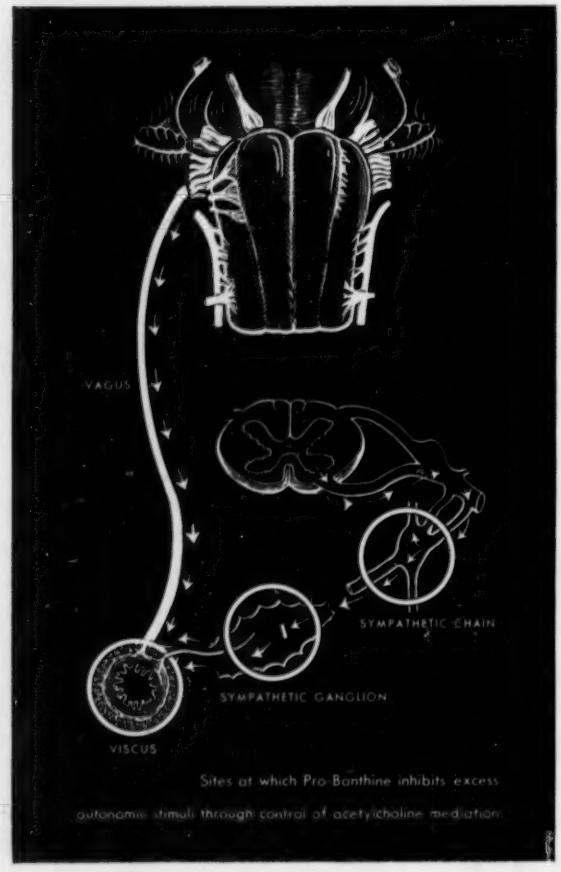
By controlling excess motility of the gastrointestinal tract, Pro-Banthine has found wide use[1] in the treatment of peptic ulcer, functional diarrheas and regional enteritis. It is also valuable in the treatment of pylorospasm and spasm of the sphincter of Oddi.




Roback and Beal[2] found that Pro-Banthine orally was an "inhibitor of spontaneous and histamine-stimulated gastric secretion" which "resulted in marked and prolonged inhibition of the motility of the stomach, jejunum, and colon . . ."

Therapy with Pro-Banthine is remarkably free from reactions associated with parasympathetic inhibition. Dryness of the mouth and blurred vision are less severe with Pro-Banthine than with certain other potent anticholinergic agents.

In Roback and Beal's[2] series "Side effects were almost entirely absent in single doses of 30 or 40 mg. . . ."

Pro-Banthine Bromide (β-diisopropylaminoethyl xanthene-9-carboxylate methobromide, brand of propantheline bromide) is available in sugar-coated tablets of 15 mg.; ampuls of 30 mg., for more rapid effects and in instances when oral medication is impractical or impossible.

For the average patient one tablet of Pro-Banthine (15 mg.) with each meal and two tablets (30 mg.) at bedtime will be adequate. G. D. Searle & Co., Research in the Service of Medicine.

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1. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: Gastroenterology *25*:416 (Nov.) 1953.

2. Roback, R. A., and Beal, J. M.: Gastroenterology *25*:24 (Sept.) 1953.

SEARLE